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(54) Title: METHOD FOR DISTINGUISHING CBF-POSITIVE AML SUBTYPES FROM CBF-NEGATIVE AML SUBTYPES

(57) Abstract: Disclosed is a method for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in a sample by determining the expression level of markers, as well as a diagnostic kit and an apparatus containing the markers.

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Method for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes

The present invention is directed to a method for distinguishing CBF (core binding factor)-positive AML subtypes, preferably AML_t(8;21) and/or AML_inv(16), from CBF-negative AML subtypes, preferably from AML_inv(3), AML_t(15;17), AML_t(11q23)/MLL (AML_MLL), and/or AML_komplext (complex aberrant karyotype) by determining the expression level of selected marker genes.

Leukemias are classified into four different groups or types: acute myeloid (AML), acute lymphatic (ALL), chronic myeloid (CML) and chronic lymphatic leukemia (CLL). Within these groups, several subcategories can be identified further using a panel of standard techniques as described below. These different subcategories in leukemias are associated with varying clinical outcome and therefore are the basis for different treatment strategies. The importance of highly specific classification may be illustrated in detail further for the AML as a very heterogeneous group of diseases. Effort is aimed at identifying biological entities and to distinguish and classify subgroups of AML which are associated with a favorable, intermediate or unfavorable prognosis, respectively. In 1976, the FAB classification was proposed by the French-American-British co-operative group which was based on cytomorphology and cytochemistry in order to separate AML subgroups according to the morphological appearance of blasts in the blood and bone marrow. In addition, it was recognized that genetic abnormalities occurring in the leukemic blast had a major impact on the morphological picture and even more on the prognosis. So far, the karyotype of the leukemic blasts is the most important independent prognostic factor regarding response to therapy as well as survival.

Usually, a combination of methods is necessary to obtain the most important information in leukemia diagnostics: Analysis of the morphology and cytochemistry of bone marrow blasts and peripheral blood cells is necessary to establish the diagnosis. In some cases the addition of immunophenotyping is mandatory to separate very undifferentiated AML from acute lymphoblastic leukemia and CLL. Leukemia subtypes investigated can be diagnosed by cytomorphology alone, only if an expert reviews the smears. However, a genetic analysis based on chromosome analysis, fluorescence in situ hybridization or RT-

PCR and immunophenotyping is required in order to assign all cases into the right category. The aim of these techniques besides diagnosis is mainly to determine the prognosis of the leukemia. A major disadvantage of these methods, however, is that viable cells are necessary as the cells for genetic analysis have to divide in vitro in order to obtain metaphases for the analysis. Another problem is the long time of 72 hours from receipt of the material in the laboratory to obtain the result. Furthermore, great experience in preparation of chromosomes and even more in analyzing the karyotypes is required to obtain the correct result in at least 90% of cases. Using these techniques in combination, hematological malignancies in a first approach are separated into chronic myeloid leukemia (CML), chronic lymphatic (CLL), acute lymphoblastic (ALL), and acute myeloid leukemia (AML). Within the latter three disease entities several prognostically relevant subtypes have been established. As a second approach this further sub-classification is based mainly on genetic abnormalities of the leukemic blasts and clearly is associated with different prognoses.

The sub-classification of leukemias becomes increasingly important to guide therapy. The development of new, specific drugs and treatment approaches requires the identification of specific subtypes that may benefit from a distinct therapeutic protocol and, thus, can improve outcome of distinct subsets of leukemia. For example, the new therapeutic drug (STI571, Imatinib) inhibits the CML specific chimeric tyrosine kinase BCR-ABL generated from the genetic defect observed in CML, the BCR-ABL-rearrangement due to the translocation between chromosomes 9 and 22 (t(9;22) (q34; q11)). In patients treated with this new drug, the therapy response is dramatically higher as compared to all other drugs that had been used so far. Another example is the subtype of acute myeloid leukemia AML M3 and its variant M3v both with karyotype t(15;17)(q22; q11-12). The introduction of a new drug (all-trans retinoic acid - ATRA) has improved the outcome in this subgroup of patient from about 50% to 85 % long-term survivors. As it is mandatory for these patients suffering from these specific leukemia subtypes to be identified as fast as possible so that the best therapy can be applied, diagnostics today must accomplish sub-classification with maximal precision. Not only for these subtypes but also for several other leukemia subtypes different treatment approaches could improve outcome. Therefore, rapid and precise identification of distinct leukemia subtypes is the future goal for diagnostics.

Thus, the technical problem underlying the present invention was to provide means for leukemia diagnostics which overcome at least some of the disadvantages of the prior art diagnostic methods, in particular encompassing the time-consuming and unreliable combination of different methods and which provides a rapid assay to unambiguously distinguish one AML subtype from another, e.g. by genetic analysis.

According to Golub et al. (Science, 1999, 286, 531-7), gene expression profiles can be used for class prediction and discriminating AML from ALL samples. However, for the analysis of acute leukemias the selection of the two different subgroups was performed using exclusively morphologic-phenotypical criteria. This was only descriptive and does not provide deeper insights into the pathogenesis or the underlying biology of the leukemia. The approach reproduces only very basic knowledge of cytomorphology and intends to differentiate classes. The data is not sufficient to predict prognostically relevant cytogenetic aberrations.

Furthermore, the international application WO-A 03/039443 discloses marker genes the expression levels of which are characteristic for certain leukemia, e.g. AML subtypes and additionally discloses methods for differentiating between the subtype of AML cells by determining the expression profile of the disclosed marker genes. However, WO-A 03/039443 does not provide guidance which set of distinct genes discriminate between two subtypes and, as such, can be routineously taken in order to distinguish one AML subtype from another.

The problem is solved by the present invention, which provides a method for distinguishing CBF-positive AML subtypes preferably AML_t(8;21) and/or AML_inv(16), from CBF-negative AML subtypes, preferably from AML_inv(3), AML_t(15;17), AML_t(11q23)/MLL, and/or AML_komplext, in a sample, the method comprising determining the expression level of markers selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2,

wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.1 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.1 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.2 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.2 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.3 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.3 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.4 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.4 having a positive fc value,

is indicative for the presence of AML_komplext when AML_komplext is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.5 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.5 having a positive fc value,

is indicative for the presence of AML_t(15;17) when AML_t(15;17) is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.1 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.1 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_MLL,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.2 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.2 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_inv(3),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.3 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.3 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.4 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.4 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.5 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.5 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_inv(3),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.6 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.6 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.7 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.7 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.8 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.8 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.9 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.9 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.10 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.10 having a positive fc value,

is indicative for the presence of AML_komplext when AML_komplext is distinguished from AML_t(15;17).

As used herein, the following definitions apply to the above ebbreviations:

CBF (core binding factor)

AML_t(8;21): AML with t(8;21) translocation

AML_inv(16): AML with inversion (16)

AML_inv(3): AML with inversion (3)

AML_t(15;17): AML with t(15;17) translocation

AML_t(11q23)/MLL (AML_MLL): AML with translocation t(11q23) in the mixed lineage leukemia gene (MLL)

AML_komplext: AML with complex aberrant karyotype

As used herein, "all other subtypes" refer to the subtypes of the present invention, i.e. if one subtype is distinguished from "all other subtypes", it is distiguished from all other subtypes contained in the present invention.

According to the present invention, a "sample" means any biological material containing genetic information in the form of nucleic acids or proteins obtainable or obtained from an individual. The sample includes e.g. tissue samples, cell samples, bone marrow and/or body fluids such as blood, saliva, semen. Preferably,

the sample is blood or bone marrow, more preferably the sample is bone marrow. The person skilled in the art is aware of methods, how to isolate nucleic acids and proteins from a sample. A general method for isolating and preparing nucleic acids from a sample is outlined in Example 3.

According to the present invention, the term "lower expression" is generally assigned to all by numbers and Affymetrix Id. definable polynucleotides the t-values and fold change (fc) values of which are negative, as indicated in the Tables. Accordingly, the term "higher expression" is generally assigned to all by numbers and Affymetrix Id. definable polynucleotides the t-values and fold change (fc) values of which are positive.

According to the present invention, the term "expression" refers to the process by which mRNA or a polypeptide is produced based on the nucleic acid sequence of a gene, i.e. „expression" also includes the formation of mRNA upon transcription. In accordance with the present invention, the term „determining the expression level" preferably refers to the determination of the level of expression, namely of the markers.

Generally, "marker" refers to any genetically controlled difference which can be used in the genetic analysis of a test versus a control sample, for the purpose of assigning the sample to a defined genotype or phenotype. As used herein, "markers" refer to genes which are differentially expressed in, e.g., different AML subtypes. The markers can be defined by their gene symbol name, their encoded protein name, their transcript identification number (cluster identification number), the data base accession number, public accession number or GenBank identifier or, as done in the present invention, Affymetrix identification number, chromosomal location, UniGene accession number and cluster type, LocusLink accession number (see Examples and Tables).

The Affymetrix identification number (affy id) is accessible for anyone and the person skilled in the art by entering the "gene expression omnibus" internet page of the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/geo/). In particular, the affy id's of the

polynucleotides used for the method of the present invention are derived from the so-called U133 chip. The sequence data of each identification number can be viewed at http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GPL96

Generally, the expression level of a marker is determined by the determining the expression of its corresponding "polynucleotide" as described hereinafter.

According to the present invention, the term „polynucleotide" refers, generally, to a DNA, in particular cDNA, or RNA, in particular a cRNA, or a portion thereof or a polypeptide or a portion thereof. In the case of RNA (or cDNA), the polynucleotide is formed upon transcription of a nucleotide sequence which is capable of expression. The polynucleotide fragments refer to fragments preferably of between at least 8, such as 10, 12, 15 or 18 nucleotides and at least 50, such as 60, 80, 100, 200 or 300 nucleotides in length, or a complementary sequence thereto, representing a consecutive stretch of nucleotides of a gene, cDNA or mRNA. In other terms, polynucleotides include also any fragment (or complementary sequence thereto) of a sequence derived from any of the markers defined above as long as these fragments unambiguously identify the marker.

The determination of the expression level may be effected at the transcriptional or translational level, i.e. at the level of mRNA or at the protein level. Protein fragments such as peptides or polypeptides advantageously comprise between at least 6 and at least 25, such as 30, 40, 80, 100 or 200 consecutive amino acids representative of the corresponding full length protein. Six amino acids are generally recognized as the lowest peptidic stretch giving rise to a linear epitope recognized by an antibody, fragment or derivative thereof. Alternatively, the proteins or fragments thereof may be analysed using nucleic acid molecules specifically binding to three-dimensional structures (aptamers).

Depending on the nature of the polynucleotide or polypeptide, the determination of the expression levels may be effected by a variety of methods. For determining and detecting the expression level, it is preferred in the present invention that the polynucleotide, in particular the cRNA, is labelled.

The labelling of the polynucleotide or a polypeptide can occur by a variety of methods known to the skilled artisan. The label can be fluorescent, chemiluminescent, bioluminescent, radioactive (such as ^{3}H or ^{32}P). The labelling compound can be any labelling compound being suitable for the labelling of polynucleotides and/or polypeptides. Examples include fluorescent dyes, such as fluorescein, dichlorofluorescein, hexachlorofluorescein, BODIPY variants, ROX, tetramethylrhodamin, rhodamin X, Cyanine-2, Cyanine-3, Cyanine-5, Cyanine-7, IRD40, FluorX, Oregon Green, Alexa variants (available e.g. from Molecular Probes or Amersham Biosciences) and the like, biotin or biotinylated nucleotides, digoxigenin, radioisotopes, antibodies, enzymes and receptors. Depending on the type of labelling, the detection is done via fluorescence measurements, conjugation to streptavidin and/or avidin, antigen-antibody- and/or antibody-antibody-interactions, radioactivity measurements, as well as catalytic and/or receptor/ligand interactions. Suitable methods include the direct labelling (incorporation) method, the amino-modified (amino-allyl) nucleotide method (available e.g. from Ambion), and the primer tagging method (DNA dendrimer labelling, as kit available e.g. from Genisphere). Particularly preferred for the present invention is the use of biotin or biotinylated nucleotides for labelling, with the latter being directly incorporated into, e.g. the cRNA polynucleotide by in vitro transcription.

If the polynucleotide is mRNA, cDNA may be prepared into which a detectable label, as exemplified above, is incorporated. Said detectably labelled cDNA, in single-stranded form, may then be hybridised, preferably under stringent or highly stringent conditions to a panel of single-stranded oligonucleotides representing different genes and affixed to a solid support such as a chip. Upon applying appropriate washing steps, those cDNAs will be detected or quantitatively detected that have a counterpart in the oligonucleotide panel. Various advantageous embodiments of this general method are feasible. For example, the mRNA or the cDNA may be amplified e.g. by polymerase chain reaction, wherein it is preferable, for quantitative assessments, that the number of amplified copies corresponds relative to further amplified mRNAs or cDNAs to the number of mRNAs originally present in the cell. In a preferred embodiment of the present invention, the cDNAs are transcribed into cRNAs prior to the hybridisation step wherein only in the transcription step a label is incorporated into the nucleic acid and wherein the cRNA is employed for hybridisation. Alternatively, the label may be attached subsequent to the transcription step.

Similarly, proteins from a cell or tissue under investigation may be contacted with a panel of aptamers or of antibodies or fragments or derivatives thereof. The antibodies etc. may be affixed to a solid support such as a chip. Binding of proteins indicative of an AML subtype may be verified by binding to a detectably labelled secondary antibody or aptamer. For the labelling of antibodies, it is referred to Harlow and Lane, "Antibodies, a laboratory manual", CSH Press, 1988, Cold Spring Harbor. Specifically, a minimum set of proteins necessary for diagnosis of all AML subtypes may be selected for creation of a protein array system to make diagnosis on a protein lysate of a diagnostic bone marrow sample directly. Protein Array Systems for the detection of specific protein expression profiles already are available (for example: Bio-Plex, BIORAD, München, Germany). For this application preferably antibodies against the proteins have to be produced and immobilized on a platform e.g. glasslides or microtiterplates. The immobilized antibodies can be labelled with a reactant specific for the certain target proteins as discussed above. The reactants can include enzyme substrates, DNA, receptors, antigens or antibodies to create for example a capture sandwich immunoassay.

For reliably distinguishing AML subtypes it is useful that the expression of more than one of the above defined markers is determined. As a criterion for the choice of markers, the statistical significance of markers as expressed in q or p values based on the concept of the false discovery rate is determined. In doing so, a measure of statistical significance called the *q* value is associated with each tested feature. The *q* value is similar to the *p* value, except it is a measure of significance in terms of the false discovery rate rather than the false positive rate (Storey JD and Tibshirani R. Proc.Natl.Acad.Sci., 2003, Vol. 100:9440-5.

In a preferred embodiment of the present invention, markers as defined in Tables 1.1-2.10 having a q-value of less than 3E-06, more preferred less than 1.5E-09, most preferred less than 1.5E-11, less than 1.5E-20, less than 1.5E-30, are measured.

Of the above defined markers, the expression level of at least two, preferably of at least ten, more preferably of at least 25, most preferably of 50 of at least one of the Tables of the markers is determined.

In another preferred embodiment, the expression level of at least 2, of at least 5, of at least 10 out of the markers having the numbers 1 – 10, 1-20, 1-40, 1-50 of at least one of the Tables are measured.

The level of the expression of the „marker", i.e. the expression of the polynucleotide is indicative of the AML subtype of a cell or an organism. The level of expression of a marker or group of markers is measured and is compared with the level of expression of the same marker or the same group of markers from other cells or samples. The comparison may be effected in an actual experiment or in silico. When the expression level also referred to as expression pattern or expression signature (expression profile) is measurably different, there is according to the invention a meaningful difference in the level of expression. Preferably the difference at least is 5 %, 10% or 20%, more preferred at least 50% or may even be as high as 75% or 100%. More preferred the difference in the level of expression is at least 200%, i.e. two fold, at least 500%, i.e. five fold, or at least 1000%, i.e. 10 fold.

Accordingly, the expression level of markers expressed lower in a first subtype than in at least one second subtype, which differs from the first subtype, is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold lower, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold lower in the first subtype. On the other hand, the expression level of markers expressed higher in a first subtype than in at least one second subtype, which differs from the first subtype, is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold higher, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold higher in the first subtype.

In another embodiment of the present invention, the sample is derived from an individual having leukaemia, preferably AML.

For the method of the present invention it is preferred if the polynucleotide the expression level of which is determined is in form of a transcribed polynucleotide. A particularly preferred transcribed polynucleotide is an mRNA, a cDNA and/or a cRNA, with the latter being preferred. Transcribed polynucleotides are isolated from a sample, reverse transcribed and/or amplified, and labelled, by employing

methods well-known the person skilled in the art (see Example 3). In a preferred embodiment of the methods according to the invention, the step of determining the expression profile further comprises amplifying the transcribed polynucleotide.

In order to determine the expression level of the transcribed polynucleotide by the method of the present invention, it is preferred that the method comprises hybridizing the transcribed polynucleotide to a complementary polynucleotide, or a portion thereof, under stringent hybridization conditions, as described hereinafter.

The term "hybridizing" means hybridization under conventional hybridization conditions, preferably under stringent conditions as described, for example, in Sambrook, J., et al., in "Molecular Cloning: A Laboratory Manual" (1989), Eds. J. Sambrook, E. F. Fritsch and T. Maniatis, Cold Spring Harbour Laboratory Press, Cold Spring Harbour, NY and the further definitions provided above. Also contemplated are polynucleotides that hybridize at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation, preferably of formamide concentration (lower percentages of formamide result in lowered stringency), salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH2PO4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 mg/ml salmon sperm blocking DNA, followed by washes at 50°C with 1 X SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5x SSC). Variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

"Complementary" and "complementarity", respectively, can be described by the percentage, i.e. proportion, of nucleotides which can form base pairs between two polynucleotide strands or within a specific region or domain of the two strands. Generally, complementary nucleotides are, according to the base pairing rules, adenine and thymine (or adenine and uracil), and cytosine and guanine. Complementarity may be partial, in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be a complete or total

complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has effects on the efficiency and strength of hybridization between nucleic acid strands.

Two nucleic acid strands are considered to be 100% complementary to each other over a defined length if in a defined region all adenines of a first strand can pair with a thymine (or an uracil) of a second strand, all guanines of a first strand can pair with a cytosine of a second strand, all thymine (or uracils) of a first strand can pair with an adenine of a second strand, and all cytosines of a first strand can pair with a guanine of a second strand, and vice versa. According to the present invention, the degree of complementarity is determined over a stretch of 20, preferably 25, nucleotides, i.e. a 60% complementarity means that within a region of 20 nucleotides of two nucleic acid strands 12 nucleotides of the first strand can base pair with 12 nucleotides of the second strand according to the above ruling, either as a stretch of 12 contiguous nucleotides or interspersed by non-pairing nucleotides, when the two strands are attached to each other over said region of 20 nucleotides. The degree of complementarity can range from at least about 50% to full, i.e. 100% complementarity. Two single nucleic acid strands are said to be "substantially complementary" when they are at least about 80% complementary, preferably about 90% or higher. For carrying out the method of the present invention substantial complementarity is preferred.

Preferred methods for detection and quantification of the amount of polynucleotides, i.e. for the methods according to the invention allowing the determination of the level of expression of a marker, are those described by Sambrook et al. (1989) or real time methods known in the art as the TaqMan® method disclosed in WO92/02638 and the corresponding U.S. 5,210,015, U.S. 5,804,375, U.S. 5,487,972. This method exploits the exonuclease activity of a polymerase to generate a signal. In detail, the (at least one) target nucleic acid component is detected by a process comprising contacting the sample with an oligonucleotide containing a sequence complementary to a region of the target nucleic acid component and a labeled oligonucleotide containing a sequence complementary to a second region of the same target nucleic acid component sequence strand, but not including the nucleic acid sequence defined by the first oligonucleotide, to create a mixture of duplexes during hybridization conditions, wherein the duplexes comprise the target nucleic acid annealed to the first oligonucleotide and to the labeled oligonucleotide such that the 3'-end of the first

oligonucleotide is adjacent to the 5'-end of the labeled oligonucleotide. Then this mixture is treated with a template-dependent nucleic acid polymerase having a 5' to 3' nuclease activity under conditions sufficient to permit the 5' to 3' nuclease activity of the polymerase to cleave the annealed, labeled oligonucleotide and release labeled fragments. The signal generated by the hydrolysis of the labeled oligonucleotide is detected and/ or measured. TaqMan® technology eliminates the need for a solid phase bound reaction complex to be formed and made detectable. Other methods include e.g. fluorescence resonance energy transfer between two adjacently hybridized probes as used in the LightCycler® format described in U.S. 6,174,670.

A preferred protocol if the marker, i.e. the polynucleotide, is in form of a transcribed nucleotide, is described in Example 3, where total RNA is isolated, cDNA and, subsequently, cRNA is synthesized and biotin is incorporated during the transcription reaction. The purified cRNA is applied to commercially available arrays which can be obtained e.g. from Affymetrix. The hybridized cRNA is detected according to the methods described in Example 3. The arrays are produced by photolithography or other methods known to experts skilled in the art e.g. from U.S. 5,445,934, U.S. 5,744,305, U.S. 5,700,637, U.S. 5,945,334 and EP 0 619 321 or EP 0 373 203, or as decribed hereinafter in greater detail.

In another embodiment of the present invention, the polynucleotide or at least one of the polynucleotides is in form of a polypeptide. In another preferred embodiment, the expression level of the polynucleotides or polypeptides is detected using a compound which specifically binds to the polynucleotide of the polypeptide of the present invention.

As used herein, "specifically binding" means that the compound is capable of discriminating between two or more polynucleotides or polypeptides, i.e. it binds to the desired polynucleotide or polypeptide, but essentially does not bind unspecifically to a different polynucleotide or polypeptide.

The compound can be an antibody, or a fragment thereof, an enzyme, a so-called small molecule compound, a protein-scaffold, preferably an anticalin. In a preferred embodiment, the compound specifically binding to the polynucleotide or polypeptide is an antibody, or a fragment thereof.

As used herein, an "antibody" comprises monoclonal antibodies as first described by Köhler and Milstein in Nature 278 (1975), 495-497 as well as polyclonal antibodies, i.e. antibodies contained in a polyclonal antiserum. Monoclonal antibodies include those produced by transgenic mice. Fragments of antibodies include $F(ab')_2$, Fab and Fv fragments. Derivatives of antibodies include scFvs, chimeric and humanized antibodies. See, for example Harlow and Lane, loc. cit. For the detection of polypeptides using antibodies or fragments thereof, the person skilled in the art is aware of a variety of methods, all of which are included in the present invention. Examples include immunoprecipitation, Western blotting, Enzyme-linked immuno sorbent assay (ELISA), Enzyme-linked immuno sorbent assay (RIA), dissociation-enhanced lanthanide fluoro immuno assay (DELFIA), scintillation proximity assay (SPA). For detection, it is desirable if the antibody is labelled by one of the labelling compounds and methods described supra.

In another preferred embodiment of the present invention, the method for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes is carried out on an array.

In general, an "array" or "microarray" refers to a linear or two- or three dimensional arrangement of preferably discrete nucleic acid or polypeptide probes which comprises an intentionally created collection of nucleic acid or polypeptide probes of any length spotted onto a substrate/solid support. The person skilled in the art knows a collection of nucleic acids or polypeptide spotted onto a substrate/solid support also under the term "array". As known to the person skilled in the art, a microarray usually refers to a miniaturised array arrangement, with the probes being attached to a density of at least about 10, 20, 50, 100 nucleic acid molecules referring to different or the same genes per cm^2. Furthermore, where appropriate an array can be referred to as "gene chip". The array itself can have different formats, e.g. libraries of soluble probes or libraries of probes tethered to resin beads, silica chips, or other solid supports.

The process of array fabrication is well-known to the person skilled in the art. In the following, the process for preparing a nucleic acid array is described. Commonly, the process comprises preparing a glass (or other) slide (e.g. chemical

treatment of the glass to enhance binding of the nucleic acid probes to the glass surface), obtaining DNA sequences representing genes of a genome of interest, and spotting sequences these sequences of interest onto glass slide. Sequences of interest can be obtained via creating a cDNA library from an mRNA source or by using publicly available databases, such as GeneBank, to annotate the sequence information of custom cDNA libraries or to identify cDNA clones from previously prepared libraries. Generally, it is recommendable to amplify obtained sequences by PCR in order to have sufficient amounts of DNA to print on the array. The liquid containing the amplified probes can be deposited on the array by using a set of microspotting pins. Ideally, the amount deposited should be uniform. The process can further include UV-crosslinking in order to enhance immobilization of the probes on the array.

In a preferred embodiment, the array is a high density oligonucleotide (oligo) array using a light-directed chemical synthesis process, employing the so-called photolithography technology. Unlike common cDNA arrays, oligo arrays (according to the Affymetrix technology) use a single-dye technology. Given the sequence information of the markers, the sequence can be synthesized directly onto the array, thus, bypassing the need for physical intermediates, such as PCR products, required for making cDNA arrays. For this purpose, the marker, or partial sequences thereof, can be represented by 14 to 20 features, preferably by less than 14 features, more preferably less than 10 features, even more preferably by 6 features or less, with each feature being a short sequence of nucleotides (oligonucleotide), which is a perfect match (PM) to a segment of the respective gene. The PM oligonucleotide are paired with mismatch (MM) oligonucleotides which have a single mismatch at the central base of the nucleotide and are used as "controls". The chip exposure sites are defined by masks and are deprotected by the use of light, followed by a chemical coupling step resulting in the synthesis of one nucleotide. The masking, light deprotection, and coupling process can then be repeated to synthesize the next nucleotide, until the nucleotide chain is of the specified length.

Advantageously, the method of the present invention is carried out in a robotics system including robotic plating and a robotic liquid transfer system, e.g. using microfluidics, i.e. channelled structured.

A particular preferred method according to the present invention is as follows:

1. Obtaining a sample, e.g. bone marrow or peripheral blood aliquots, from a patient having AML
2. Extracting RNA, preferably mRNA, from the sample
3. Reverse transcribing the RNA into cDNA
4. In vitro transcribing the cDNA into cRNA
5. Fragmenting the cRNA
6. Hybridizing the fragmented cRNA on standard microarrays
7. Determining hybridization

In another embodiment, the present invention is directed to the use of at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, for the manufacturing of a diagnostic for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes. The use of the present invention is particularly advantageous for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in an individual having AML. The use of said markers for diagnosis of CBF-positive AML subtypes from CBF-negative AML subtypes, preferably based on microarray technology, offers the following advantages: (1) more rapid and more precise diagnosis, (2) easy to use in laboratories without specialized experience, (3) abolishes the requirement for analyzing viable cells for chromosome analysis (transport problem), and (4) very experienced hematologists for cytomorphology and cytochemistry, immunophenotyping as well as cytogeneticists and molecularbiologists are no longer required.

Accordingly, the present invention refers to a diagnostic kit containing at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes, in combination with suitable auxiliaries. Suitable auxiliaries, as used herein, include buffers, enzymes, labelling compounds, and the like. In a preferred embodiment, the marker contained in the kit is a nucleic acid molecule which is capable of hybridizing to the mRNA corresponding to at least one marker of the present invention. Preferably, the at least one nucleic acid molecule is attached to a solid support, e.g. a polystyrene microtiter dish, nitrocellulose membrane, glass surface or to non-immobilized particles in solution.

In another preferred embodiment, the diagnostic kit contains at least one reference for a CBF-positive AML subtype and/or a CBF-negative AML subtype. As used herein, the reference can be a sample or a data bank.

In another embodiment, the present invention is directed to an apparatus for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in a sample, containing a reference data bank obtainable by comprising

(a) compiling a gene expression profile of a patient sample by determining the expression level at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, and

(b) classifying the gene expression profile by means of a machine learning algorithm.

According to the present invention, the "machine learning algorithm" is a computational-based prediction methodology, also known to the person skilled in the art as "classifier", employed for characterizing a gene expression profile. The signals corresponding to a certain expression level which are obtained by the microarray hybridization are subjected to the algorithm in order to classify the expression profile. Supervised learning involves "training" a classifier to recognize the distinctions among classes and then "testing" the accuracy of the classifier on an independent test set. For new, unknown sample the classifier shall predict into which class the sample belongs.

Preferably, the machine learning algorithm is selected from the group consisting of Weighted Voting, K-Nearest Neighbors, Decision Tree Induction, Support Vector Machines (SVM), and Feed-Forward Neural Networks. Most preferably, the machine learning algorithm is Support Vector Machine, such as polynomial kernel and Gaussian Radial Basis Function-kernel SVM models.

The classification accuracy of a given gene list for a set of microarray experiments is preferably estimated using Support Vector Machines (SVM), because there is evidence that SVM-based prediction slightly outperforms other classification techniques like k-Nearest Neighbors (k-NN). The LIBSVM software package version 2.36 was used (SVM-type: C-SVC, linear kernel (http://www.csie.ntu.edu.tw/~cjlin/libsvm/)). The skilled artisan is furthermore referred to Brown et al., Proc.Natl.Acad.Sci., 2000; 97: 262-267, Furey et al.,

Bioinformatics. 2000; 16: 906-914, and Vapnik V. Statistical Learning Theory. New York: Wiley, 1998.

In detail, the classification accuracy of a given gene list for a set of microarray experiments can be estimated using Support Vector Machines (SVM) as supervised learning technique. Generally, SVMs are trained using differentially expressed genes which were identified on a subset of the data and then this trained model is employed to assign new samples to those trained groups from a second and different data set. Differentially expressed genes were identified applying ANOVA and t-test-statistics (Welch t-test). Based on identified distinct gene expression signatures respective training sets consisting of 2/3 of cases and test sets with 1/3 of cases to assess classification accuracies are designated. Assignment of cases to training and test set is randomized and balanced by diagnosis. Based on the training set a Support Vector Machine (SVM) model is built.

According to the present invention, the apparent accuracy, i.e. the overall rate of correct predictions of the complete data set was estimated by 10fold cross validation. This means that the data set was divided into 10 approximately equally sized subsets, an SVM-model was trained for 9 subsets and predictions were generated for the remaining subset. This training and prediction process was repeated 10 times to include predictions for each subset. Subsequently the data set was split into a training set, consisting of two thirds of the samples, and a test set with the remaining one third. Apparent accuracy for the training set was estimated by 10fold cross validation (analogous to apparent accuracy for complete set). A SVM-model of the training set was built to predict diagnosis in the independent test set, thereby estimating true accuracy of the prediction model. This prediction approach was applied both for overall classification (multi-class) and binary classification (diagnosis X => yes or no). For the latter, sensitivity and specificity were calculated:

Sensitivity = (number of positive samples predicted)/(number of true positives)

Specificity = (number of negative samples predicted)/(number of true negatives)

In a preferred embodiment, the reference data bank is backed up on a computational data memory chip which can be inserted in as well as removed from

the apparatus of the present invention, e.g. like an interchangeable module, in order to use another data memory chip containing a different reference data bank.

The apparatus of the present invention containing a desired reference data bank can be used in a way such that an unknown sample is, first, subjected to gene expression profiling, e.g. by microarray analysis in a manner as described supra or in the art, and the expression level data obtained by the analysis are, second, fed into the apparatus and compared with the data of the reference data bank obtainable by the above method. For this purpose, the apparatus suitably contains a device for entering the expression level of the data, for example a control panel such as a keyboard. The results, whether and how the data of the unknown sample fit into the reference data bank can be made visible on a provided monitor or display screen and, if desired, printed out on an incorporated of connected printer.

Alternatively, the apparatus of the present invention is equipped with particular appliances suitable for detecting and measuring the expression profile data and, subsequently, proceeding with the comparison with the reference data bank. In this embodiment, the apparatus of the present invention can contain a gripper arm and/or a tray which takes up the microarray containing the hybridized nucleic acids.

In another embodiment, the present invention refers to a reference data bank for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in a sample obtainable by comprising

(a) compiling a gene expression profile of a patient sample by determining the expression level of at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, and

(b) classifying the gene expression profile by means of a machine learning algorithm.

Preferably, the reference data bank is backed up and/or contained in a computational memory data chip.

The invention is further illustrated in the following table and examples, without limiting the scope of the invention:

TABLES 1.1-2.10

Tables 1.1-2.10 show AML subtype analysis of CBF (core binding factor)-positive AML subtypes, preferably AML_t(8;21) and AML_inv(16), from CBF-negative AML subtypes, preferably from AML_inv(3), AML_t(15;17), AML_t(11q23)/MLL, and/or AML_komplext (complex aberrant karyotype). The analysed markers are ordered according to their q-values, beginning with the lowest q-values.

For convenience and a better understanding, Tables 1.1 to 2.10 are accompanied with explanatory tables (Table 1.1A to 2.10A) where the numbering and the Affymetrix Id are further defined by other parameters, e.g. gene bank accession number.

EXAMPLES

Example 1: General experimental design of the invention and results

The core binding factor (CBF) subunits CBFα2 and CBFβ are frequently involved in acute myeloid leukemias. The CBFα2 subunit, also designated AML1 (RUNX1), is affected by the translocation t(8;21). The beta subunit is affected by an inversion of chromosome 16 generating several variants of CBFβ-MYH11 fusion proteins. CBF oncoproteins have been proven excellent markers for cytogenetically based prognostification as well as monitoring of minimal residual disease. However, little is known about common CBF targets and their relevance for leukemogenic mechanisms. Here, we analyzed comprehensive gene expression signatures of a representative cohort of AML patients by use of microarrays (U133set, Affymetrix). First, gene signatures of 50 CBF positive cases, n=25 samples with t(8;21) and inv(16) each, were compared to other balanced chromomsomal aberrations (inv(3) (n=18), t(15;17) (n=20), t(11q23)/MLL (n=31)), as well as AML with complex aberrant karyotypes (n=34). Differentially expressed genes identified from a respective training set consisting of 2/3 of cases were applied to built a Support Vector Machine (SVM) model. Subsequently, classification accuracy was assessed in the remaining 1/3 of the cases. SVM subtype stratification accurately predicts all 51/51 independent test samples. Thus, CBF

leukemias share common gene signatures. Among the top 50 genes distinguishing CBF leukemias from other AML subsets three interesting candidates were identified. The transcription factor CCAAT/enhancer binding protein alpha, encoded by the CEBPA gene, was found to be lower expressed in t(8;21) cases. This confirms the data from Pabst et al. demonstrating that AML1-ETO expression downregulated CEBPA mRNA, protein and DNA binding activity. Furthermore, we observed that also in inv(16) CBF leukemias CEBPA expression is downregulated. Secondly, Copine VIII was found downregulated in CBF leukemias. More detailed, Copine VIII expression was calculated as absent in t(8;21) and inv(16) samples. Copine VIII has recently been described as novel fusion partner of AML1 in an aggressive AML with t(12;21) translocation. AML1 was fused out of frame with Copine VIII resulting in an abnormal translational termination of Copine VIII. The truncated AML1 protein only contained the DNA-binding but not the transactivation domain. It has been speculated that disruption of Copine VIII expression confers an additional proliferative mutation. Here, our data suggests that CBF leukemias do not express Copine VIII at all. Finally, RUNX3 (AML2) was identified to be downregulated in CBF leukemias. RUNX3 has been reported to play a functional role in the nervous system and lack of RUNX3 is causally related to the genesis and progression of human gastric cancer. According to our data, it can be speculated that RUNX3 expression is also silenced in CBF leukemias due to hypermethylation of CpG islands in the promotor region as demonstrated for mouse carcinoma cell lines. Moreover, lack of Copine VIII as well as downregulated RUNX3 expression was also observed when CBF leukemias were compared to AML with normal karyotypes (n=159) as well as to 51 cases with unbalanced chromosomal aberrations: trisomy 8 (n=12), trisomy 11 (n=7), trisomy 13 (n=7), monosomy 7 (n=9), del(5q) (n=7) and del(9q) (n=9). In conclusion, besides previous reported distinct signatures for t(8;21) and inv(16) cases, common expression patterns caused by CBF oncoproteins could be identified. Future studies will have to focus on those common CBF targets and functional assays need to be established proving their leukemogenic relevance.

Example 2: General materials, methods and definitions of functional annotations

The methods section contains both information on statistical analyses used for identification of differentially expressed genes and detailed annotation data of identified microarray probesets.

Affymetrix Probeset Annotation

All annotation data of GeneChip® arrays are extracted from the NetAffx™ Analysis Center (internet website: www.affymetrix.com). Files for U133 set arrays, including U133A and U133B microarrays are derived from the June 2003 release. The original publication refers to: Liu G, Loraine AE, Shigeta R, Cline M, Cheng J, Valmeekam V, Sun S, Kulp D, Siani-Rose MA. NetAffx: Affymetrix probesets and annotations. Nucleic Acids Res. 2003;31(1):82-6.

The sequence data are omitted due to their large size, and because they do not change, whereas the annotation data are updated periodically, for example new information on chromomal location and functional annotation of the respective gene products. Sequence data are available for download in the NetAffx Download Center (www.affymetrix.com)

Data fields:

In the following section, the content of each field of the data files are described. Microarray probesets, for example found to be differentially expressed between different types of leukemia samples are further described by additional information. The fields are of the following types:

1. GeneChip Array Information
2. Probe Design Information
3. Public Domain and Genomic References

1. GeneChip Array Information

HG-U133 ProbeSet_ID:

HG-U133 ProbeSet_ID describes the probe set identifier. Examples are: 200007_at, 200011_s_at, 200012_x_at.

GeneChip:
The description of the GeneChip probe array name where the respective probeset is represented. Examples are: Affymetrix Human Genome U133A Array or Affymetrix Human Genome U133B Array.

2. Probe Design Information

Sequence Type:
The Sequence Type indicates whether the sequence is an Exemplar, Consensus or Control sequence. An Exemplar is a single nucleotide sequence taken directly from a public database. This sequence could be an mRNA or EST. A Consensus sequence, is a nucleotide sequence assembled by Affymetrix, based on one or more sequence taken from a public database.

Transcript ID:
The cluster identification number with a sub-cluster identifier appended.

Sequence Derived From:
The accession number of the single sequence, or representative sequence on which the probe set is based. Refer to the "Sequence Source" field to determine the database used.

Sequence ID:
For Exemplar sequences: Public accession number or GenBank identifier. For Consensus sequences: Affymetrix identification number or public accession number.

Sequence Source:
The database from which the sequence used to design this probe set was taken. Examples are: GenBank®, RefSeq, UniGene, TIGR (annotations from The Institute for Genomic Research).

3. Public Domain and Genomic References

Most of the data in this section come from LocusLink and UniGene databases, and are annotations of the reference sequence on which the probe set is modeled.

Gene Symbol and Title:
A gene symbol and a short title, when one is available. Such symbols are assigned by different organizations for different species. Affymetrix annotational data come from the UniGene record. There is no indication which species-specific databank was used, but some of the possibilities include for example HUGO: The Human Genome Organization.

MapLocation:
The map location describes the chromosomal location when one is available.

Unigene_Accession:
UniGene accession number and cluster type. Cluster type can be "full length" or "est", or "---" if unknown.

LocusLink:
This information represents the LocusLink accession number.

Full Length Ref. Sequences:
Indicates the references to multiple sequences in RefSeq. The field contains the ID and description for each entry, and there can be multiple entries per probeSet.

Example 3: Sample preparation, processing and data analysis

Method 1:

Microarray analyses were performed utilizing the GeneChip® System (Affymetrix, Santa Clara, USA). Hybridization target preparations were performed according to recommended protocols (Affymetrix Technical Manual). In detail, at time of diagnosis, mononuclear cells were purified by Ficoll-Hypaque density centrifugation. They had been lysed immediately in RLT buffer (Qiagen, Hilden, Germany), frozen, and stored at -80°C from 1 week to 38 months. For gene expression profiling cell lysates of the leukemia samples were thawed, homogenized (QIAshredder, Qiagen), and total RNA was extracted (RNeasy Mini Kit, Qiagen). Subsequently, 5-10 µg total RNA isolated from 1 x 10^7 cells was used as starting material for cDNA synthesis with oligo$[(dT)_{24}$T7promotor$]_{65}$ primer (cDNA Synthesis System, Roche Applied Science, Mannheim, Germany).

cDNA products were purified by phenol/chlorophorm/IAA extraction (Ambion, Austin, USA) and acetate/ethanol-precipitated overnight. For detection of the hybridized target nucleic acid biotin-labeled ribonucleotides were incorporated during the following *in vitro* transcription reaction (Enzo BioArray HighYield RNA Transcript Labeling Kit, Enzo Diagnostics). After quantification by spectrophotometric measurements and 260/280 absorbance values assessment for quality control of the purified cRNA (RNeasy Mini Kit, Qiagen), 15 µg cRNA was fragmented by alkaline treatment (200 mM Tris-acetate, pH 8.2/500 mM potassium acetate/150 mM magnesium acetate) and added to the hybridization cocktail sufficient for five hybridizations on standard GeneChip microarrays (300 µl final volume). Washing and staining of the probe arrays was performed according to the recommended Fluidics Station protocol (EukGE-WS2v4). Affymetrix Microarray Suite software (version 5.0.1) extracted fluorescence signal intensities from each feature on the microarrays as detected by confocal laser scanning according to the manufacturer's recommendations.

Expression analysis quality assessment parameters included visiual array inspection of the scanned image for the presence of image artifacts and correct grid alignment for the identification of distinct probe cells as well as both low 3'/5' ratio of housekeeping controls (mean: 1.90 for GAPDH) and high percentage of detection calls (mean: 46.3% present called genes). The 3' to 5' ratio of GAPDH probesets can be used to assess RNA sample and assay quality. Signal values of the 3' probe sets for GAPDH are compared to the Signal values of the corresponding 5' probe set. The ratio of the 3' probe set to the 5' probe set is generally no more than 3.0. A high 3' to 5' ratio may indicate degraded RNA or inefficient synthesis of ds cDNA or biotinylated cRNA (GeneChip® Expression Analysis Technical Manual, www.affymetrix.com). Detection calls are used to determine whether the transcript of a gene is detected (present) or undetected (absent) and were calculated using default parameters of the Microarray Analysis Suite MAS 5.0 software package.

Method 2:

Bone marrow (BM) aspirates are taken at the time of the initial diagnostic biopsy and remaining material is immediately lysed in RLT buffer (Qiagen), frozen and stored at -80 C until preparation for gene expression analysis. For microarray analysis the GeneChip System (Affymetrix, Santa Clara, CA, USA) is used. The

targets for GeneChip analysis are prepared according to the current Expression Analysis. Briefly, frozen lysates of the leukemia samples are thawed, homogenized (QIAshredder, Qiagen) and total RNA extracted (RNeasy Mini Kit, Qiagen).Normally 10 ug total RNA isolated from 1 x 107 cells is used as starting material in the subsequent cDNA-Synthesis using Oligo-dT-T7-Promotor Primer (cDNA synthesis Kit, Roche Molecular Biochemicals). The cDNA is purified by phenol-chlorophorm extraction and precipitated with 100% Ethanol over night. For detection of the hybridized target nucleic acid biotin-labeled ribonucleotides are incorporated during the in vitro transcription reaction (Enzo® BioArray™ HighYield™ RNA Transcript Labeling Kit, ENZO). After quantification of the purified cRNA (RNeasy Mini Kit, Qiagen), 15 ug are fragmented by alkaline treatment (200 mM Tris-acetate, pH 8.2, 500 mM potassium acetate, 150 mM magnesium acetate) and added to the hybridization cocktail sufficient for 5 hybridizations on standard GeneChip microarrays. Before expression profiling Test3 Probe Arrays (Affymetrix) are chosen for monitoring of the integrity of the cRNA. Only labeled cRNA-cocktails which showed a ratio of the messured intensity of the 3' to the 5' end of the GAPDH gene less than 3.0 are selected for subsequent hybridization on HG-U133 probe arrays (Affymetrix). Washing and staining the Probe arrays is performed as described (siehe Affymetrix-Original-Literatur (LOCKHART und LIPSHUTZ). The Affymetrix software (Microarray Suite, Version 4.0.1) extracted fluorescence intensities from each element on the arrays as detected by confocal laser scanning according to the manufacturers recommendations.

Claims

1. A method for distinguishing CBF-positive AML subtypes, preferably AML_t(8;21) and/or AML_inv(16) from CBF-negative AML subtypes, preferably AML_inv(3), AML_t(15;17), AML_t(11q23)/MLL (AML_MLL), and/or AML_komplext, in a sample, the method comprising determining the expression level of markers selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2,

wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.1 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.1 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.2 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.2 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.3 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.3 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.4 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.4 having a positive fc value,

is indicative for the presence of AML_komplext when AML_komplext is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.5 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 1.5 having a positive fc value,

is indicative for the presence of AML_t(15;17) when AML_t(15;17) is distinguished from all other subtypes,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.1 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.1 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_MLL,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.2 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.2 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_inv(3),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.3 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.3 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.4 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.4 having a positive fc value,

is indicative for the presence of AML_CBF when AML_CBF is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.5 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.5 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_inv(3),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.6 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.6 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.7 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.7 having a positive fc value,

is indicative for the presence of AML_MLL when AML_MLL is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.8 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.8 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from AML_komplext,

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.9 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.9 having a positive fc value,

is indicative for the presence of AML_inv(3) when AML_inv(3) is distinguished from AML_t(15;17),

and/or wherein

a lower expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.10 having a negative fc value, and/or

a higher expression of at least one polynucleotide defined by at least one of the numbers 1 to 50 of Table 2.10 having a positive fc value,

is indicative for the presence of AML_komplext when AML_komplext is distinguished from AML_t(15;17).

2. The method according to claim 1 wherein the polynucleotide is labelled.

3. The method according to claim 1 or 2, wherein the label is a luminescent, preferably a fluorescent label, an enzymatic or a radioactive label.

4. The method according at least one of the claims 1-3, wherein the expression level of at least two, preferably of at least ten, more preferably of at least 25, most preferably of 50 of the markers of at least one of the Tables 1.1-2.10 is determined.

5. The method according to at least one of the claims 1-4, wherein the expression level of markers expressed lower in a first subtype than in at least one second subtype, which differs from the first subtype, is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold lower, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold lower in the first subtype.

6. The method according to at least one of the claims 1-4, wherein the expression level of markers expressed higher in a first subtype than in at least one second subtype, which differs from the first subtype, is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold higher, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold higher in the first subtype.

7. The method according to at least one of the claims 1-6, wherein the sample is from an individual having AML.

8. The method according to at least one of the claims 1-7, wherein at least one polynucleotide is in the form of a transcribed polynucleotide, or a portion thereof.

9. The method according to claim 8, wherein the transcribed polynucleotide is a mRNA or a cDNA.

10. The method according to claim 8 or 9, wherein the determining of the expression level comprises hybridizing the transcribed polynucleotide to a complementary polynucleotide, or a portion thereof, under stringent hybridization conditions.

11. The method according to at least one of the claims 1-7, wherein at least one polynucleotide is in the form of a polypeptide, or a portion thereof.

12. The method according to at least one of the claims 8, 9 or 12, wherein the determining of the expression level comprises contacting the polynucleotide or the polypeptide with a compound specifically binding to the polynucleotide or the polypeptide.

13. The method according to claim 12, wherein the compound is an antibody, or a fragment thereof.

14. The method according to at least one of the claims 1-13, wherein the method is carried out on an array.

15. The method according to at least one of the claims 1-14, wherein the method is carried out in a robotics system.

16. The method according to at least one of the claims 1-15, wherein the method is carried out using microfluidics.

17. Use of at least one marker as defined in at least one of the claims 1-3 for the manufacturing of a diagnostic for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes.

18. The use according to claim 17 for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes.

19. A diagnostic kit containing at least one marker as defined in at least one of the claims 1-3 for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes, in combination with suitable auxiliaries.

20. The diagnostic kit according to claim 19, wherein the kit contains a reference for the CBF-positive AML subtype and/ or the CBF-negative AML subtype.

21. The diagnostic kit according to claim 20, wherein the reference is a sample or a data bank.

22. An apparatus for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in a sample containing a reference data bank.

23. The apparatus according to claim 22, wherein the reference data bank is obtainable by comprising

(a) compiling a gene expression profile of a patient sample by determining the expression level of at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, and

(b) classifying the gene expression profile by means of a machine learning algorithm.

24. The apparatus according to claim 23, wherein the machine learning algorithm is selected from the group consisting of Weighted Voting, K-Nearest Neighbors, Decision Tree Induction, Support Vector Machines, and Feed-Forward Neural Networks, preferably Support Vector Machines.

25. The apparatus according to at least one of the claims 22-24, wherein the apparatus contains a control panel and/or a monitor.

26. A reference data bank for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes obtainable by comprising

(a) compiling a gene expression profile of a patient sample by determining the expression level of at least one marker selected from the markers identifiable by their Affymetrix Identification Numbers (affy id) as defined in Tables 1, and/or 2, and

(b) classifying the gene expression profile by means of a machine learning algorithm.

27. The reference data bank according to claim 26, wherein the reference data bank is backed up and/or contained in a computational memory chip.

Table 1

1. One-Versus-All (OVA)								
1.1	AML_CBF versus rest							
#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	224998_at	CKLFSF4	-2.20	1.12E-22	2.46E-18	-0.95	-11.71	16q21
2	204198_s_at	RUNX3	-4.24	1.02E-21	1.12E-17	-0.92	-11.33	1p36
3	217963_s_at	NGFRAP1	-17.14	1.44E-19	1.06E-15	-1.00	-11.10	Xq22.1
4	214651_s_at	HOXA9	-21.04	9.39E-19	3.32E-15	-0.97	-10.76	7p15-p14
5	241706_at	LOC144402	-4.85	1.05E-18	3.32E-15	-0.87	-10.42	12q11
6	204197_s_at	RUNX3	-3.28	1.03E-18	3.32E-15	-0.85	-10.34	1p36
7	228058_at	LOC124220	2.68	7.94E-17	1.17E-13	0.90	10.29	16p13.3
8	212895_s_at	ABR	-2.27	4.71E-19	2.60E-15	-0.83	-10.26	17p13.3
9	213908_at		-8.28	6.66E-17	1.05E-13	-0.90	-9.94	
10	206847_s_at	HOXA7	-4.17	4.34E-17	8.70E-14	-0.84	-9.87	7p15-p14
11	203379_at	RPS6KA1	-2.15	7.80E-18	2.15E-14	-0.79	-9.82	3
12	215087_at		-2.55	1.80E-17	4.41E-14	-0.79	-9.71	
13	225009_at	CKLFSF4	-3.66	8.94E-17	1.23E-13	-0.82	-9.68	16q21
14	218608_at	HSA9947	-4.03	2.89E-17	6.37E-14	-0.78	-9.63	1p36
15	235753_at		-7.51	4.38E-16	4.39E-13	-0.89	-9.61	
16	217975_at	LOC51186	-7.65	2.71E-16	3.14E-13	-0.82	-9.56	Xq22.1
17	228365_at	LOC144402	-6.72	2.45E-16	3.00E-13	-0.81	-9.54	12q11
18	220558_x_at	PHEMX	-1.78	5.80E-17	9.83E-14	-0.76	-9.46	11p15.5
19	203949_at	MPO	1.99	5.58E-17	9.83E-14	0.76	9.45	17q23.1
20	233467_s_at	PHEMX	-1.82	1.48E-16	1.91E-13	-0.75	-9.30	11p15.5
21	223299_at	LOC90701	-2.04	3.34E-16	3.67E-13	-0.75	-9.23	18q21.31
22	204000_at	GNB5	-2.25	3.77E-16	3.96E-13	-0.75	-9.21	15q15.3
23	202178_at	PRKCZ	-6.84	8.06E-16	7.72E-13	-0.74	-9.11	1p36.33-p36.2
24	209905_at	HOXA9	-59.65	6.93E-15	4.93E-12	-0.86	-9.09	7p15-p14
25	213147_at	HOXA10	-4.59	1.50E-15	1.27E-12	-0.75	-9.06	7p15-p14
26	238756_at		-2.94	1.28E-15	1.18E-12	-0.74	-9.05	
27	205760_s_at	OGG1	-2.41	1.50E-15	1.27E-12	-0.72	-8.94	3p26.2
28	203741_s_at	ADCY7	-3.08	2.67E-15	2.18E-12	-0.72	-8.89	16q12-q13
29	52975_at	FLJ00001	-2.15	3.50E-15	2.70E-12	-0.71	-8.78	9q34.11
30	221581_s_at	WBSCR5	-2.85	3.56E-15	2.70E-12	-0.70	-8.76	7q11.23
31	204495_s_at	DKFZP434H132	-2.45	6.20E-15	4.55E-12	-0.70	-8.66	15q22.33
32	226586_at	FLJ36928	-2.17	9.71E-15	6.68E-12	-0.69	-8.59	9q22.33
33	213353_at	ABCA5	-2.42	1.58E-14	1.05E-11	-0.69	-8.53	17q24.3
34	243010_at	MSI2	-2.24	5.29E-14	2.99E-11	-0.72	-8.51	17q23.1
35	211031_s_at	CYLN2	-3.67	3.60E-14	2.21E-11	-0.69	-8.46	7q11.23
36	235391_at	LOC137392	-4.46	1.05E-13	5.52E-11	-0.72	-8.43	8q21.3
37	232636_at	DKFZp547M2010	-4.24	3.07E-14	1.99E-11	-0.68	-8.43	Xq27.3
38	224839_s_at	GPT2	-4.15	4.82E-14	2.87E-11	-0.69	-8.42	16q12.1

39	213150_at	HOXA10	-7.84	8.93E-14	4.80E-11	-0.70	-8.38	7p15-p14
40	222987_s_at	TMEM9	-1.44	3.60E-14	2.21E-11	-0.67	-8.37	
41	202887_s_at	RTP801	-2.64	5.54E-14	3.05E-11	-0.67	-8.32	10pter-q26.12
42	203188_at	B3GNT6	-1.65	5.24E-14	2.99E-11	-0.67	-8.31	11q13.1
43	213241_at		-3.48	1.10E-13	5.64E-11	-0.68	-8.26	
44	201811_x_at	SH3BP5	-4.42	2.55E-13	1.15E-10	-0.70	-8.25	3p24.3
45	230894_s_at		-5.34	2.58E-13	1.15E-10	-0.69	-8.21	
46	225240_s_at		-2.96	2.03E-13	9.71E-11	-0.68	-8.20	
47	226134_s_at		-3.24	2.38E-13	1.12E-10	-0.68	-8.19	
48	201700_at	CCND3	-1.90	1.27E-13	6.37E-11	-0.65	-8.14	6p21
49	220560_at	C11orf21	-2.42	1.91E-13	9.36E-11	-0.65	-8.08	11p15.5
50	37408_at	MRC2	-2.36	2.72E-13	1.17E-10	-0.66	-8.08	17q23.3
1.2	AML_MLL versus rest							
#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	202746_at	ITM2A	-11.87	5.73E-34	1.18E-29	-1.31	-16.09	Xq13.3-Xq21.2
2	201830_s_at	NET1	-4.57	2.16E-32	2.23E-28	-1.22	-15.22	10p15
3	202747_s_at	ITM2A	-12.16	8.61E-32	5.93E-28	-1.22	-15.13	Xq13.3-Xq21.2
4	201829_at	NET1	-2.89	1.31E-27	6.75E-24	-1.08	-13.43	10p15
5	200953_s_at	CCND2	-3.65	6.66E-27	2.29E-23	-1.08	-13.32	12p13
6	225831_at	LOC148894	-3.76	6.08E-27	2.29E-23	-1.07	-13.26	1p36.11
7	226517_at	BCAT1	-9.69	8.03E-25	2.37E-21	-1.03	-12.63	12pter-q12
8	225653_at		-1.93	9.80E-25	2.53E-21	-1.01	-12.52	
9	200951_s_at	CCND2	-4.19	4.36E-24	1.00E-20	-0.98	-12.19	12p13
10	225344_at	ERAP140	-4.57	8.97E-23	1.68E-19	-0.96	-11.76	6q22.33
11	218966_at	MYO5C	-2.65	5.13E-23	1.06E-19	-0.94	-11.73	15q21
12	214651_s_at	HOXA9	5.18	7.62E-15	1.77E-12	1.21	11.53	7p15-p14
13	235818_at		-8.30	2.81E-22	4.84E-19	-0.92	-11.45	
14	225285_at		-8.04	1.75E-21	2.78E-18	-0.89	-11.14	
15	214390_s_at	BCAT1	-8.28	4.51E-21	6.65E-18	-0.90	-11.10	12pter-q12
16	200602_at	APP	-8.23	5.14E-21	7.07E-18	-0.88	-10.97	21q21.3
17	200665_s_at	SPARC	-7.09	6.57E-21	8.48E-18	-0.88	-10.95	5q31.3-q32
18	227297_at		-11.30	6.91E-20	6.80E-17	-0.90	-10.82	
19	211137_s_at	ATP2C1	-2.27	3.86E-20	4.20E-17	-0.86	-10.70	3q21-q24
20	219188_s_at	LRP16	-3.60	3.06E-20	3.72E-17	-0.86	-10.69	11q11
21	213549_at	PRO2730	-3.50	3.49E-20	4.01E-17	-0.86	-10.69	3p21.31
22	203544_s_at	STAM	-3.11	5.12E-20	5.29E-17	-0.86	-10.66	10p14-p13
23	218041_x_at	SLC38A2	-1.73	9.32E-15	2.09E-12	-1.02	-10.61	12q
24	214439_x_at	BIN1	-2.96	7.32E-19	6.05E-16	-0.87	-10.58	2q14
25	212558_at	SPRY1	-4.05	1.32E-19	1.19E-16	-0.84	-10.46	4q27
26	219271_at	GalNac-T10	-5.87	1.22E-19	1.15E-16	-0.84	-10.45	2p23.1
27	206761_at	TACTILE	-12.89	2.40E-18	1.71E-15	-0.88	-10.29	3q13.13

28	213737_x_at		2.00	1.02E-13	1.76E-11	1.03	10.26	
29	220306_at	FLJ20202	-4.14	5.04E-19	4.34E-16	-0.83	-10.25	1p11.1
30	235753_at		5.24	3.02E-12	3.14E-10	1.23	10.24	
31	231259_s_at	CCND2	-2.31	7.32E-18	4.41E-15	-0.84	-10.19	12p13
32	219686_at	HSA250839	-10.50	4.76E-18	3.07E-15	-0.87	-10.15	4p16.2
33	214643_x_at	BIN1	-3.29	2.37E-18	1.71E-15	-0.82	-10.13	2q14
34	213147_at	HOXA10	4.22	3.73E-12	3.74E-10	1.19	10.08	7p15-p14
35	214953_s_at	APP	-5.12	2.13E-18	1.63E-15	-0.81	-10.08	21q21.3
36	227584_at		-3.12	1.82E-18	1.45E-15	-0.81	-10.05	
37	222780_s_at	BAALC	-5.21	7.65E-18	4.41E-15	-0.84	-10.01	8q22.3
38	220104_at	ZAP	-2.69	2.75E-18	1.88E-15	-0.81	-10.00	7q34
39	204082_at	PBX3	5.98	1.49E-11	1.24E-09	1.36	9.97	9q33-q34
40	209362_at	SURB7	-1.83	1.20E-16	4.44E-14	-0.84	-9.96	12p11.23
41	221832_s_at	LOC148894	-2.76	1.50E-17	7.92E-15	-0.82	-9.96	1p36.11
42	209543_s_at	CD34	-6.34	2.82E-18	1.88E-15	-0.80	-9.95	1q32
43	201015_s_at	JUP	-5.25	5.65E-17	2.24E-14	-0.83	-9.95	17q21
44	210201_x_at	BIN1	-2.47	2.04E-17	9.97E-15	-0.81	-9.88	2q14
45	206009_at	ITGA9	-2.93	9.65E-18	5.39E-15	-0.80	-9.87	3p21.3
46	221760_at	MAN1A1	-6.54	1.24E-17	6.74E-15	-0.81	-9.86	6q22
47	218899_s_at	BAALC	-7.37	1.98E-17	9.95E-15	-0.83	-9.86	8q22.3
48	223075_s_at	IBA2	-3.77	6.94E-18	4.35E-15	-0.79	-9.83	9q34.13-q34.3
49	226473_at	LOC147136	-3.01	1.71E-17	8.85E-15	-0.80	-9.81	17q25.3
50	224049_at	KCNK17	-2.99	7.68E-18	4.41E-15	-0.79	-9.78	6p21.1
1.3	AML_inv(3) versus rest							
#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	205382_s_at	DF	-5.56	5.89E-23	1.44E-18	-0.95	-11.78	19p13.3
2	212318_at	TRN-SR	-2.30	8.43E-19	4.13E-15	-1.01	-11.72	7q32.2
3	210115_at	RPL39L	-7.32	2.23E-21	2.73E-17	-0.92	-11.23	3q27
4	200700_s_at	KDELR2	-2.59	6.00E-17	1.77E-13	-0.98	-11.19	7p22.2
5	204921_at	GAS8	-3.02	3.34E-21	2.73E-17	-0.89	-11.06	16q24.3
6	204301_at	KIAA0711	-8.14	1.10E-19	6.77E-16	-0.85	-10.54	8p23.2
7	203949_at	MPO	-3.59	2.09E-15	3.56E-12	-0.89	-10.23	17q23.1
8	205131_x_at	SCGF	-6.54	1.56E-18	6.39E-15	-0.81	-10.04	19q13.3
9	209122_at	ADFP	-3.26	5.65E-16	1.16E-12	-0.85	-10.04	9p21.3
10	211709_s_at	SCGF	-3.76	5.33E-13	3.72E-10	-0.92	-9.87	19q13.3
11	223703_at	CDA017	-2.37	1.10E-16	2.45E-13	-0.81	-9.84	10q23.1
12	210783_x_at	SCGF	-6.06	2.95E-17	1.03E-13	-0.77	-9.58	19q13.3
13	203948_s_at	MPO	-4.43	3.40E-15	4.90E-12	-0.81	-9.55	17q23.1
14	204647_at	HOMER3	-3.83	6.50E-17	1.77E-13	-0.77	-9.55	19p13.11
15	228293_at	LOC91614	-5.75	6.24E-15	8.05E-12	-0.81	-9.49	11p13
16	202487_s_at	H2AV	-1.94	4.75E-11	1.66E-08	-0.95	-9.44	7p13
17	202954_at	UBE2C	-2.40	2.88E-15	4.42E-12	-0.79	-9.43	20q13.11

18	231300_at	LOC90835	-2.82	4.09E-15	5.57E-12	-0.79	-9.42	16p11.2
19	201186_at	LRPAP1	-2.34	9.17E-15	1.12E-11	-0.80	-9.39	4p16.3
20	203421_at	PIG11	-4.30	1.04E-16	2.45E-13	-0.75	-9.35	11p11.2
21	205248_at	C21orf5	-1.85	3.75E-13	2.87E-10	-0.82	-9.27	21q22.2
22	226789_at		-2.35	1.57E-13	1.28E-10	-0.81	-9.24	
23	223609_at	ASP	-2.48	1.04E-14	1.20E-11	-0.77	-9.20	2p11.2
24	202605_at	GUSB	-2.34	2.07E-11	8.60E-09	-0.87	-9.12	7q21.11
25	230480_at	HIWI2	-2.94	1.07E-15	2.02E-12	-0.74	-9.11	11q21
26	202185_at	PLOD3	-1.85	8.56E-13	5.38E-10	-0.81	-9.06	7q22
27	231736_x_at	MGST1	-3.17	2.36E-12	1.32E-09	-0.81	-9.02	12p12.3-p12.1
28	230044_at		-2.76	4.97E-13	3.58E-10	-0.79	-8.99	
29	203591_s_at	CSF3R	-2.66	6.26E-14	6.13E-11	-0.75	-8.91	1p35-p34.3
30	210140_at	CST7	-3.80	2.18E-15	3.56E-12	-0.72	-8.89	20p11.21
31	208795_s_at	MCM7	-2.07	6.37E-12	3.22E-09	-0.81	-8.87	7q21.3-q22.1
32	227429_at	MGC45840	-2.30	5.47E-13	3.72E-10	-0.76	-8.80	11p15.5
33	227165_at	C13orf3	-1.88	7.09E-13	4.70E-10	-0.76	-8.72	13q11
34	221739_at	IL27w	-1.71	2.23E-10	5.63E-08	-0.85	-8.67	19p13.3
35	216640_s_at	P5	-2.21	1.08E-11	4.90E-09	-0.78	-8.60	2p25.1
36	204548_at	STAR	-7.36	1.08E-14	1.20E-11	-0.69	-8.58	8p11.2
37	224918_x_at	MGST1	-2.95	6.50E-11	2.21E-08	-0.80	-8.56	12p12.3-p12.1
38	226123_at	LOC286180	-3.18	2.61E-13	2.06E-10	-0.72	-8.56	8q12.1
39	226071_at	DKFZP434K1772	-2.96	1.91E-14	2.03E-11	-0.68	-8.48	1q21.2
40	200078_s_at - HG-U133A	ATP6V0B	-1.88	8.78E-10	1.64E-07	-0.86	-8.46	1p32.3
41	201580_s_at	DJ971N18.2	-1.91	2.38E-12	1.32E-09	-0.73	-8.44	20p12
42	211048_s_at	ERP70	-2.33	1.30E-12	7.96E-10	-0.72	-8.43	7q35
43	218681_s_at	SDF2L1	-2.14	5.66E-14	5.79E-11	-0.69	-8.42	22q11.21
44	218829_s_at	KIAA1416	-2.35	1.04E-13	9.81E-11	-0.69	-8.41	8q12.1
45	225002_s_at	DKFZP566I1024	-2.16	8.62E-10	1.64E-07	-0.83	-8.32	7q11.1
46	204332_s_at	AGA	-1.67	1.05E-11	4.85E-09	-0.72	-8.25	4q32-q33
47	201940_at	CPD	-1.93	6.93E-12	3.40E-09	-0.71	-8.23	17p11.1-q11.2
48	217770_at	PIGT	-1.73	1.93E-10	5.15E-08	-0.77	-8.22	20q12-q13.12
49	203675_at	NUCB2	-2.16	4.33E-11	1.56E-08	-0.74	-8.22	11p15.1-p14
50	206589_at	GFI1	-3.21	2.09E-10	5.46E-08	-0.77	-8.20	1p22
1.4	AML_komplext versus rest							
#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	223318_s_at	MGC10974	-3.31	9.11E-24	1.10E-19	-0.97	-12.08	19p13.3
2	200608_s_at	RAD21	1.76	6.44E-15	1.55E-11	1.07	10.89	8q24
3	227056_at		-2.48	1.79E-19	1.08E-15	-0.89	-10.82	

4	222229_x_at		-1.42	1.84E-14	3.70E-11	-1.04	-10.59	
5	202413_s_at	USP1	1.91	1.91E-13	1.92E-10	1.07	10.31	1p32.1-p31.3
6	205382_s_at	DF	-3.93	4.77E-19	1.92E-15	-0.82	-10.25	19p13.3
7	201377_at	NICE-4	2.10	2.11E-12	1.36E-09	1.14	10.02	1q21.3
8	209190_s_at	DIAPH1	-2.04	1.60E-16	4.84E-13	-0.76	-9.41	5q31
9	209523_at	TAF2	2.40	1.16E-11	4.27E-09	1.03	9.31	8q24.12
10	212232_at	FNBP4	1.72	9.27E-12	3.73E-09	0.95	9.10	11p11.12
11	222902_s_at	FLJ21144	1.75	5.62E-12	2.61E-09	0.92	9.09	1p34.1
12	218436_at	SIL1	-2.51	8.04E-14	8.83E-11	-0.79	-9.00	5q31
13	217846_at	QARS	-1.51	2.14E-12	1.36E-09	-0.85	-8.94	3p21.3-p21.1
14	209022_at	STAG2	1.85	2.29E-11	7.28E-09	0.95	8.94	Xq25
15	224481_s_at	HECTD1	1.62	2.29E-11	7.28E-09	0.92	8.82	14q12
16	203079_s_at	CUL2	2.05	3.30E-11	9.28E-09	0.93	8.78	10p11.21
17	200093_s_at - HG-U133B	HINT1	-1.63	5.11E-12	2.47E-09	-0.83	-8.73	5q31.2
18	202406_s_at	TIAL1	1.58	4.59E-11	1.18E-08	0.93	8.71	10q
19	208645_s_at	RPS14	-1.28	1.91E-11	6.59E-09	-0.85	-8.58	5q31-q33
20	227878_s_at	MGC10974	-1.56	6.33E-14	7.65E-11	-0.71	-8.58	19p13.3
21	216032_s_at	SDBCAG84	-2.10	4.12E-14	7.11E-11	-0.70	-8.53	20pter-q12
22	203519_s_at	UPF2	1.96	1.00E-10	2.28E-08	0.90	8.47	10p14-p13
23	223592_s_at	MGC13061	-1.93	4.84E-14	7.31E-11	-0.69	-8.45	17q11.2
24	218331_s_at	FLJ20360	1.98	1.23E-10	2.60E-08	0.90	8.41	10p15.1
25	212058_at	SR140	1.69	1.74E-10	3.34E-08	0.91	8.38	3q23
26	214700_x_at	DKFZP434D193	2.48	4.42E-10	7.26E-08	0.99	8.35	2q23.3
27	202659_at	PSMB10	-2.31	1.06E-12	8.00E-10	-0.72	-8.32	16q22.1
28	233168_s_at	IMAGE3510317	1.60	5.29E-11	1.33E-08	0.82	8.30	22q13.33
29	213514_s_at	DIAPH1	-2.20	5.82E-14	7.65E-11	-0.67	-8.30	5q31
30	212463_at		3.56	5.90E-10	9.25E-08	1.01	8.30	
31	213682_at	NUP50	1.74	1.70E-10	3.31E-08	0.87	8.27	22q13.31
32	217729_s_at	AES	-1.91	2.55E-13	2.37E-10	-0.68	-8.21	19p13.3
33	201807_at	VPS26	1.73	1.11E-10	2.39E-08	0.83	8.20	10q21.1
34	209259_s_at	CSPG6	1.95	3.62E-10	6.24E-08	0.90	8.19	10q25
35	201352_at	YME1L1	1.61	2.00E-10	3.63E-08	0.86	8.18	10p14
36	200094_s_at - HG-U133B	EEF2	-1.36	1.03E-11	4.02E-09	-0.74	-8.17	19pter-q12
37	218040_at	FLJ10330	1.86	3.04E-10	5.32E-08	0.87	8.14	1p13.2
38	239071_at		1.60	2.63E-11	7.93E-09	0.76	8.13	
39	223591_at	MGC13061	-1.75	3.85E-13	3.32E-10	-0.66	-8.11	17q11.2
40	200984_s_at	CD59	2.81	8.46E-10	1.26E-07	0.95	8.10	11p13
41	218577_at	FLJ20331	1.85	3.75E-10	6.29E-08	0.83	7.97	1p31.1
42	206003_at	KIAA0635	1.92	2.09E-10	3.70E-08	0.79	7.95	4q12
43	208646_at	RPS14	-2.03	7.38E-12	3.07E-09	-0.68	-7.89	5q31-q33
44	218600_at	MGC10986	-1.99	2.63E-12	1.53E-09	-0.66	-7.88	17q24.1
45	201360_at	CST3	-2.67	9.31E-13	7.49E-10	-0.64	-7.87	20p11.21
46	218917_s_at	SMARCF1	1.80	1.11E-09	1.47E-07	0.87	7.85	1p35.3
47	201498_at	USP7	1.89	1.41E-09	1.74E-07	0.89	7.83	16p13.3

48	208826_x_at	HINT1	-1.40	7.93E-11	1.87E-08	-0.73	-7.83	5q31.2
49	223276_at	NID67	-1.89	6.77E-12	2.92E-09	-0.66	-7.81	5q33.1
50	200985_s_at	CD59	3.64	2.10E-09	2.30E-07	0.92	7.81	11p13
1.5	AML_t(15;17) versus rest							
#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	211990_at	HLA-DPA1	-10.42	4.21E-49	7.95E-45	-1.78	-22.09	6p21.3
2	209732_at	CLECSF2	-34.05	2.99E-46	2.82E-42	-1.80	-21.72	12p13-p12
3	201923_at	PRDX4	-7.30	2.26E-39	1.42E-35	-1.50	-18.49	Xp22.13
4	204425_at	ARHGAP4	-16.74	1.59E-38	7.50E-35	-1.45	-17.83	Xq28
5	205771_s_at	AKAP7	-9.68	2.85E-35	1.08E-31	-1.31	-16.30	6q23
6	200931_s_at	VCL	-4.09	2.77E-31	5.23E-28	-1.31	-15.91	10q22.1-q23
7	214450_at	CTSW	7.86	6.54E-13	2.63E-11	2.45	15.88	11q13.1
8	211474_s_at	SERPINB6	-4.37	5.15E-32	1.21E-28	-1.28	-15.72	6p25
9	227353_at	EVER2	-3.92	3.55E-25	2.16E-22	-1.36	-15.67	17q25.3
10	204661_at	CDW52	-19.47	8.52E-33	2.68E-29	-1.25	-15.47	1p36
11	38487_at	STAB1	8.83	1.62E-12	6.04E-11	2.50	15.40	3p21.31
12	201137_s_at	HLA-DPB1	-10.31	1.47E-32	3.96E-29	-1.24	-15.38	6p21.3
13	217478_s_at	HLA-DMA	-5.26	1.08E-30	1.70E-27	-1.25	-15.34	6p21.3
14	212953_x_at	CALR	3.10	5.60E-13	2.28E-11	2.11	15.18	19p13.3-p13.2
15	217848_s_at	PP	-3.56	3.36E-24	1.54E-21	-1.30	-15.01	10q11.1-q24
16	227598_at	LOC113763	-3.99	3.01E-29	3.78E-26	-1.23	-14.98	7q35
17	213587_s_at	LOC155066	-5.19	2.06E-31	4.32E-28	-1.20	-14.90	7q36.1
18	208306_x_at	HLA-DRB4	-6.81	7.24E-29	8.53E-26	-1.21	-14.79	6p21.3
19	34210_at	CDW52	-24.96	9.96E-31	1.70E-27	-1.20	-14.77	1p36
20	236554_x_at	EVER2	-3.72	4.52E-26	3.22E-23	-1.24	-14.75	17q25.3
21	203535_at	S100A9	-7.39	1.67E-27	1.66E-24	-1.21	-14.64	1q21
22	221004_s_at	ITM2C	4.51	3.65E-13	1.58E-11	1.86	14.57	2q37
23	203948_s_at	MPO	2.82	1.81E-17	2.11E-15	1.39	14.34	17q23.1
24	204362_at	SCAP2	-10.94	7.03E-30	1.02E-26	-1.15	-14.26	7p21-p15
25	211991_s_at	HLA-DPA1	-15.52	2.25E-29	3.02E-26	-1.15	-14.21	6p21.3
26	209312_x_at	HLA-DRB1	-6.22	1.01E-26	8.69E-24	-1.17	-14.19	6p21.3
27	200654_at	P4HB	2.09	1.32E-14	8.02E-13	1.49	13.85	17q25
28	221865_at	DKFZp547P234	-3.19	2.67E-24	1.29E-21	-1.14	-13.64	9q33.1
29	225639_at	SCAP2	-9.13	3.33E-27	2.99E-24	-1.10	-13.55	7p21-p15
30	238949_at	FLJ31951	-7.68	1.56E-27	1.63E-24	-1.09	-13.51	5q33.3
31	241742_at	PRAM-1	-6.88	1.27E-27	1.41E-24	-1.08	-13.44	19p13.2
32	232617_at	CTSS	-5.12	1.95E-27	1.83E-24	-1.08	-13.37	1q21
33	208982_at	PECAM1	-4.42	1.65E-26	1.36E-23	-1.06	-13.14	17q23
34	238022_at		6.24	1.40E-11	4.18E-10	1.90	13.12	
35	227999_at	LOC170394	-2.87	1.83E-19	3.20E-17	-1.17	-13.12	10q26.3
36	223280_x_at	MS4A6A	-14.76	4.62E-26	3.22E-23	-1.07	-13.08	11q12.1

37	216899_s_at	SCAP2	-5.23	3.80E-26	2.99E-23	-1.05	-13.02	7p21-p15
38	204670_x_at	HLA-DRB5	-5.19	1.54E-20	3.33E-18	-1.13	-12.96	6p21.3
39	208892_s_at	DUSP6	-5.59	3.69E-23	1.42E-20	-1.08	-12.95	12q22-q23
40	229041_s_at		-21.00	1.64E-25	1.06E-22	-1.07	-12.92	
41	204319_s_at	RGS10	-4.08	4.35E-26	3.22E-23	-1.04	-12.90	10q25
42	204361_s_at	SCAP2	-7.94	2.37E-25	1.49E-22	-1.04	-12.87	7p21-p15
43	209288_s_at	CDC42EP3	-8.17	6.25E-26	4.20E-23	-1.03	-12.81	2p21
44	204046_at	PLCB2	-5.14	4.73E-22	1.51E-19	-1.08	-12.79	15q15
45	205382_s_at	DF	3.00	1.70E-13	7.96E-12	1.39	12.78	19p13.3
46	224356_x_at	MS4A6A	-14.81	4.05E-25	2.39E-22	-1.05	-12.75	11q12.1
47	209619_at	CD74	-4.16	1.25E-17	1.49E-15	-1.17	-12.74	5q32
48	201753_s_at	ADD3	-5.17	1.18E-24	5.87E-22	-1.04	-12.73	10q24.2-q24.3
49	226077_at	FLJ31951	-5.28	4.99E-25	2.85E-22	-1.03	-12.68	5q33.3
50	221059_s_at	CHST6	-4.46	4.86E-24	2.13E-21	-1.03	-12.64	16q22

Table 2

2. All-Pairs (AP)

2.1 AML_CBF versus AML_MLL

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	214651_s_at	HOXA9	-39.94	3.41E-16	1.52E-12	-2.37	-15.03	7p15-p14
2	235753_at		-14.90	1.42E-13	1.58E-10	-1.99	-12.16	
3	213147_at	HOXA10	-8.59	7.86E-14	1.00E-10	-1.64	-11.79	7p15-p14
4	206847_s_at	HOXA7	-7.43	2.51E-13	2.48E-10	-1.74	-11.67	7p15-p14
5	213737_x_at		-2.55	9.62E-17	8.57E-13	-1.34	-11.62	
6	203949_at	MPO	3.71	8.37E-16	2.79E-12	1.36	11.51	17q23.1
7	226517_at	BCAT1	9.76	2.84E-16	1.51E-12	1.38	11.48	12pter-q12
8	228058_at	LOC124220	5.61	2.19E-18	5.86E-14	1.26	11.44	16p13.3
9	209905_at	HOXA9	-127.68	2.13E-12	1.54E-09	-1.85	-10.98	7p15-p14
10	201830_s_at	NET1	4.03	1.39E-16	9.30E-13	1.25	10.97	10p15
11	221581_s_at	WBSCR5	-4.41	1.01E-13	1.23E-10	-1.38	-10.88	7q11.23
12	225831_at	LOC148894	3.38	8.67E-17	8.57E-13	1.19	10.74	1p36.11
13	202746_at	ITM2A	11.33	5.01E-15	9.55E-12	1.31	10.72	Xq13.3-Xq21.2
14	219271_at	GalNac-T10	7.41	1.27E-15	3.40E-12	1.23	10.62	2p23.1
15	227297_at		15.56	1.77E-14	2.78E-11	1.35	10.58	
16	235818_at		11.01	1.05E-14	1.74E-11	1.24	10.36	
17	213908_at		-15.79	9.00E-12	4.71E-09	-1.67	-10.34	
18	203948_s_at	MPO	4.07	4.49E-15	9.23E-12	1.16	10.23	17q23.1
19	202747_s_at	ITM2A	11.55	2.55E-14	3.79E-11	1.23	10.18	Xq13.3-Xq21.2
20	200953_s_at	CCND2	3.19	1.06E-15	3.14E-12	1.12	10.12	12p13
21	201015_s_at	JUP	6.14	7.37E-16	2.79E-12	1.11	10.08	17q21

22	206009_at	ITGA9	3.55	3.54E-15	7.88E-12	1.13	10.03	3p21.3
23	214452_at	BCAT1	3.68	2.20E-15	5.35E-12	1.12	10.03	12pter-q12
24	225285_at		8.06	9.72E-15	1.73E-11	1.13	9.94	
25	204082_at	PBX3	-5.96	1.40E-11	6.69E-09	-1.44	-9.92	9q33-q34
26	218899_s_at	BAALC	6.90	2.17E-13	2.23E-10	1.21	9.73	8q22.3
27	229215_at	ASCL2	-5.29	2.72E-12	1.82E-09	-1.22	-9.70	11p15.5
28	214390_s_at	BCAT1	8.90	1.39E-13	1.58E-10	1.16	9.69	12pter-q12
29	213150_at	HOXA10	-15.06	3.49E-11	1.43E-08	-1.39	-9.57	7p15-p14
30	239272_at	MMP28	7.09	5.89E-13	5.07E-10	1.16	9.44	17q11-q21.1
31	203733_at	MYLE	-2.93	1.48E-11	6.93E-09	-1.24	-9.43	16p13.2
32	225653_at		1.85	4.85E-14	6.82E-11	1.05	9.37	
33	218041_x_at	SLC38A2	1.67	4.48E-13	4.28E-10	1.06	9.22	12q
34	201828_x_at	CXX1	-2.45	1.29E-12	1.01E-09	-1.07	-9.15	Xq26
35	229817_at	KIAA1281	2.68	6.03E-14	8.05E-11	1.01	9.13	5q23.2
36	227853_at		-2.41	4.13E-12	2.63E-09	-1.08	-9.08	
37	223299_at	LOC90701	-2.56	7.56E-12	4.21E-09	-1.09	-9.03	18q21.31
38	201829_at	NET1	2.65	5.29E-13	4.85E-10	1.04	9.02	10p15
39	201564_s_at	FSCN1	4.07	1.86E-13	1.99E-10	0.99	8.91	7p22
40	220104_at	ZAP	2.72	5.45E-13	4.85E-10	0.99	8.80	7q34
41	200665_s_at	SPARC	9.43	5.67E-12	3.44E-09	1.06	8.75	5q31.3-q32
42	201105_at	LGALS1	-3.06	6.39E-12	3.71E-09	-1.02	-8.74	22q13.1
43	209543_s_at	CD34	6.99	3.62E-12	2.36E-09	1.02	8.68	1q32
44	216264_s_at	LAMB2	2.28	7.05E-13	5.89E-10	0.94	8.56	3p21
45	202719_s_at	TES	2.79	9.35E-13	7.57E-10	0.94	8.54	7q31.2
46	200951_s_at	CCND2	3.68	2.40E-12	1.65E-09	0.96	8.49	12p13
47	229744_at		2.16	2.19E-12	1.54E-09	0.95	8.46	
48	241756_at		2.95	1.76E-12	1.34E-09	0.93	8.42	
49	201153_s_at	MBNL1	-1.85	4.28E-11	1.73E-08	-1.00	-8.38	3q25
50	201152_s_at	MBNL1	-1.98	8.23E-11	2.62E-08	-1.01	-8.33	3q25

2.2 AML_CBF versus AML_inv(3)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	203949_at	MPO	4.97	2.50E-21	6.79E-17	2.20	17.29	17q23.1
2	203948_s_at	MPO	5.93	9.48E-21	1.29E-16	1.77	14.42	17q23.1
3	205382_s_at	DF	5.98	3.26E-17	2.96E-13	1.43	11.63	19p13.3
4	210755_at	HGF	5.52	1.90E-15	1.29E-11	1.34	10.77	7q21.1
5	211709_s_at	SCGF	3.97	1.63E-13	8.83E-10	1.33	10.46	19q13.3
6	217963_s_at	NGFRAP1	-27.42	1.99E-08	9.03E-06	-2.04	-9.76	Xq22.1
7	210997_at	HGF	18.82	4.77E-13	1.85E-09	1.27	9.63	7q21.1
8	228058_at	LOC124220	2.35	3.23E-13	1.46E-09	1.11	9.13	16p13.3
9	228293_at	LOC91614	7.55	5.67E-13	1.93E-09	1.09	8.99	11p13
10	210115_at	RPL39L	8.39	4.95E-12	1.22E-08	1.19	8.98	3q27
11	203591_s_at	CSF3R	3.01	9.49E-13	2.87E-09	1.07	8.81	1p35-p34.3
12	209122_at	ADFP	3.10	3.22E-12	8.73E-09	1.04	8.58	9p21.3

13	202605_at	GUSB	2.23	3.39E-10	3.84E-07	1.13	8.55	7q21.11
14	205131_x_at	SCGF	5.91	1.27E-11	2.65E-08	1.03	8.36	19q13.3
15	235818_at		4.36	8.70E-12	1.97E-08	1.02	8.34	
16	231736_x_at	MGST1	3.05	6.85E-11	1.24E-07	1.03	8.23	12p12.3-p12.1
17	222955_s_at	HT011	1.98	1.81E-11	3.52E-08	0.99	8.13	Xq26.1
18	202185_at	PLOD3	1.73	2.32E-10	3.07E-07	1.03	8.10	7q22
19	224918_x_at	MGST1	2.87	3.97E-10	4.31E-07	1.04	8.09	12p12.3-p12.1
20	202887_s_at	RTP801	-3.54	1.24E-07	3.47E-05	-1.29	-7.92	10pter-q26.12
21	202487_s_at	H2AV	1.85	9.85E-10	8.10E-07	1.02	7.89	7p13
22	210150_s_at	LAMA5	2.99	8.18E-11	1.39E-07	0.94	7.74	20q13.2-q13.3
23	210783_x_at	SCGF	5.67	1.53E-10	2.32E-07	0.95	7.72	19q13.3
24	221218_s_at	TPK1	2.42	1.36E-10	2.18E-07	0.93	7.62	7q34-q35
25	206871_at	ELA2	3.63	2.75E-10	3.33E-07	0.93	7.61	19p13.3
26	212318_at	TRN-SR	2.02	1.66E-10	2.37E-07	0.92	7.56	7q32.2
27	226789_at		2.25	2.38E-10	3.07E-07	0.92	7.55	
28	209960_at	HGF	9.81	6.23E-10	6.51E-07	0.96	7.52	7q21.1
29	200078_s_at - HG-U133A	ATP6V0B	1.87	2.12E-09	1.60E-06	0.96	7.52	1p32.3
30	210998_s_at	HGF	10.77	7.53E-10	7.06E-07	0.97	7.50	7q21.1
31	200700_s_at	KDELR2	2.32	2.82E-10	3.33E-07	0.90	7.44	7p22.2
32	200078_s_at - HG-U133B	ATP6V0B	1.87	2.34E-09	1.68E-06	0.94	7.43	1p32.3
33	213908_at		-4.43	6.38E-07	1.09E-04	-1.32	-7.38	
34	206855_s_at	HYAL2	1.88	7.35E-10	7.06E-07	0.91	7.38	3p21.3
35	204548_at	STAR	5.65	9.51E-10	8.07E-07	0.90	7.28	8p11.2
36	233467_s_at	PHEMX	-2.16	4.63E-07	9.78E-05	-1.19	-7.27	11p15.5
37	205248_at	C21orf5	1.79	7.09E-10	7.06E-07	0.89	7.27	21q22.2
38	217975_at	LOC51186	-13.60	1.23E-06	1.76E-04	-1.49	-7.25	Xq22.1
39	230896_at		-19.80	1.28E-06	1.81E-04	-1.53	-7.25	
40	212895_s_at	ABR	-2.33	3.15E-07	7.43E-05	-1.13	-7.24	17p13.3
41	241525_at	LOC200772	24.74	2.62E-09	1.82E-06	0.97	7.23	2q37.3
42	202990_at	PYGL	2.69	8.62E-10	7.80E-07	0.88	7.22	14q21-q22
43	204193_at	CHKL	1.89	9.13E-10	8.00E-07	0.88	7.21	22q13.33
44	204198_s_at	RUNX3	-4.49	6.28E-07	1.09E-04	-1.20	-7.18	1p36
45	204647_at	HOMER3	3.73	1.17E-09	9.33E-07	0.88	7.18	19p13.11
46	208308_s_at	GPI	2.20	2.03E-09	1.58E-06	0.88	7.13	19q13.1
47	220668_s_at	DNMT3B	-3.79	1.17E-06	1.69E-04	-1.29	-7.10	20q11.2
48	201811_x_at	SH3BP5	-7.94	1.55E-06	2.06E-04	-1.42	-7.10	3p24.3
49	227212_s_at		1.91	5.67E-09	3.42E-06	0.89	7.08	
50	206478_at	KIAA0125	-10.45	1.81E-06	2.33E-04	-1.43	-7.03	14q32.33

2.3 AML_CBF versus AML_komplext

#	affy Id	HUGO name	fc	p	q	stn	t	Map Location
1	222229_x_at		1.45	1.33E-15	8.31E-12	1.33	11.26	

2	209619_at	CD74	2.23	7.59E-17	9.49E-13	1.15	10.50	5q32
3	206847_s_at	HOXA7	-3.87	9.61E-13	1.03E-09	-1.36	-10.35	7p15-p14
4	217846_at	QARS	1.63	3.83E-15	1.59E-11	1.16	10.24	3p21.3-p21.1
5	209523_at	TAF2	-2.87	3.40E-13	5.31E-10	-1.19	-9.89	8q24.12
6	205382_s_at	DF	3.91	5.71E-15	1.78E-11	1.08	9.77	19p13.3
7	213147_at	HOXA10	-3.95	5.75E-13	7.98E-10	-1.12	-9.53	7p15-p14
8	212463_at		-5.62	1.99E-11	8.01E-09	-1.30	-9.49	
9	202406_s_at	TIAL1	-1.72	1.07E-12	1.03E-09	-1.13	-9.48	10q
10	200984_s_at	CD59	-3.98	1.88E-11	8.01E-09	-1.26	-9.41	11p13
11	202413_s_at	USP1	-1.90	2.92E-13	5.21E-10	-1.08	-9.37	1p32.1-p31.3
12	218040_at	FLJ10330	-2.18	4.02E-12	2.51E-09	-1.13	-9.29	1p13.2
13	200608_s_at	RAD21	-1.73	8.03E-14	1.67E-10	-1.03	-9.28	8q24
14	211423_s_at	SC5DL	-2.71	1.55E-12	1.29E-09	-1.10	-9.26	11q23.3
15	241706_at	LOC144402	-5.96	5.03E-11	1.66E-08	-1.27	-9.20	12q11
16	200985_s_at	CD59	-6.72	3.92E-11	1.33E-08	-1.24	-9.19	11p13
17	227056_at		2.52	6.44E-14	1.61E-10	1.00	9.12	
18	212232_at	FNBP4	-1.82	1.28E-12	1.14E-09	-1.05	-9.10	11p11.12
19	217963_s_at	NGFRAP1	-22.83	1.93E-10	4.31E-08	-1.40	-8.98	Xq22.1
20	201807_at	VPS26	-1.96	1.74E-12	1.30E-09	-1.03	-8.96	10q21.1
21	201377_at	NICE-4	-1.96	1.09E-11	5.26E-09	-1.08	-8.93	1q21.3
22	224481_s_at	HECTD1	-1.71	2.19E-12	1.52E-09	-1.03	-8.92	14q12
23	209022_at	STAG2	-1.95	4.92E-12	2.93E-09	-1.04	-8.85	Xq25
24	201663_s_at	SMC4L1	-2.83	1.09E-10	2.99E-08	-1.18	-8.80	3q26.1
25	203079_s_at	CUL2	-2.21	5.34E-12	3.03E-09	-1.02	-8.78	10p11.21
26	222902_s_at	FLJ21144	-1.79	3.45E-12	2.27E-09	-1.01	-8.77	1p34.1
27	214651_s_at	HOXA9	-21.57	3.34E-10	6.15E-08	-1.35	-8.76	7p15-p14
28	203948_s_at	MPO	2.58	1.06E-12	1.03E-09	0.97	8.70	17q23.1
29	204198_s_at	RUNX3	-5.72	1.79E-10	4.31E-08	-1.18	-8.68	1p36
30	203949_at	MPO	2.08	7.92E-12	4.12E-09	1.00	8.63	17q23.1
31	235753_at		-6.60	4.98E-10	8.52E-08	-1.34	-8.63	
32	206003_at	KIAA0635	-2.18	8.29E-12	4.15E-09	-1.00	-8.63	4q12
33	201920_at	SLC20A1	-2.22	2.33E-11	9.10E-09	-1.01	-8.51	2q11-q14
34	210982_s_at	HLA-DRA	2.58	8.99E-13	1.03E-09	0.92	8.45	6p21.3
35	218577_at	FLJ20331	-2.06	1.97E-11	8.01E-09	-0.98	-8.42	1p31.1
36	201352_at	YME1L1	-1.73	1.42E-11	6.56E-09	-0.97	-8.39	10p14
37	203519_s_at	UPF2	-2.04	3.69E-11	1.28E-08	-0.98	-8.35	10p14-p13
38	207332_s_at	TFRC	-2.51	1.91E-10	4.31E-08	-1.06	-8.34	3q26.2-qter
39	208894_at	HLA-DRA	2.78	1.77E-12	1.30E-09	0.91	8.33	6p21.3
40	203965_at	USP20	-1.95	2.72E-11	1.00E-08	-0.95	-8.24	9q34.13
41	212058_at	SR140	-1.75	5.66E-11	1.81E-08	-0.96	-8.20	3q23
42	235521_at	HOXA3	-6.52	1.37E-09	1.73E-07	-1.20	-8.18	7p15-p14
43	208886_at	H1F0	-4.09	5.36E-10	8.79E-08	-1.06	-8.15	22q13.1
44	212491_s_at	DNAJC8	-1.59	7.26E-11	2.21E-08	-0.95	-8.10	1p35.2
45	223575_at	KIAA1549	2.50	6.81E-12	3.70E-09	0.89	8.09	7q34
46	201498_at	USP7	-2.04	1.90E-10	4.31E-08	-0.97	-8.06	16p13.3
47	218331_s_at	FLJ20360	-1.99	1.31E-10	3.41E-08	-0.95	-8.02	10p15.1

48	203092_at	TIMM44	-3.39	5.46E-10	8.79E-08	-1.00	-7.99	19p13.3-p13.2
49	200620_at	C1orf8	-1.51	1.60E-10	4.00E-08	-0.95	-7.98	1p36-p31
50	218754_at	FLJ23323	-1.74	3.04E-10	5.66E-08	-0.97	-7.96	1p36.23

2.4 AML_CBF versus AML_t(15;17)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	211990_at	HLA-DPA1	12.12	1.17E-32	3.01E-28	2.88	23.66	6p21.3
2	209732_at	CLECSF2	31.14	1.05E-28	1.35E-24	3.06	23.26	12p13-p12
3	214450_at	CTSW	-12.43	2.71E-13	9.29E-11	-2.99	-16.77	11q13.1
4	38487_at	STAB1	-11.88	9.92E-13	2.65E-10	-2.95	-15.94	3p21.31
5	217478_s_at	HLA-DMA	6.54	6.42E-24	5.49E-20	1.91	15.86	6p21.3
6	201923_at	PRDX4	7.01	6.69E-23	4.30E-19	1.83	15.19	Xp22.13
7	226878_at		4.73	2.79E-22	1.19E-18	1.82	14.96	
8	209312_x_at	HLA-DRB1	7.81	9.84E-23	5.05E-19	1.78	14.82	6p21.3
9	209619_at	CD74	5.09	3.15E-21	1.01E-17	1.78	14.62	5q32
10	201137_s_at	HLA-DPB1	13.79	1.00E-19	2.14E-16	1.85	14.34	6p21.3
11	211991_s_at	HLA-DPA1	21.30	1.24E-19	2.45E-16	1.85	14.30	6p21.3
12	208306_x_at	HLA-DRB4	8.24	1.17E-21	4.31E-18	1.72	14.28	6p21.3
13	211474_s_at	SERPINB6	5.43	1.65E-20	4.71E-17	1.71	13.95	6p25
14	221004_s_at	ITM2C	-4.01	5.11E-13	1.58E-10	-2.10	-13.90	2q37
15	203535_at	S100A9	8.36	3.42E-20	7.98E-17	1.58	13.19	1q21
16	204670_x_at	HLA-DRB5	6.20	2.55E-20	6.54E-17	1.57	13.17	6p21.3
17	212953_x_at	CALR	-2.63	3.62E-13	1.15E-10	-1.88	-13.10	19p13.3-p13.2
18	201719_s_at	EPB41L2	13.15	1.21E-17	1.63E-14	1.63	12.69	6q23
19	227353_at	EVER2	3.71	2.62E-19	4.81E-16	1.51	12.64	17q25.3
20	204661_at	CDW52	25.58	2.79E-17	3.41E-14	1.63	12.54	1p36
21	208689_s_at	RPN2	-1.78	3.04E-14	1.52E-11	-1.64	-12.34	20q12-q13.1
22	228113_at	STAT3	4.04	5.73E-19	9.80E-16	1.47	12.31	17q21
23	215193_x_at	HLA-DRB1	7.74	7.80E-19	1.25E-15	1.47	12.27	6p21.3
24	205663_at	PCBP3	-4.65	3.38E-11	5.70E-09	-1.99	-12.20	21q22.3
25	205771_s_at	AKAP7	7.09	5.93E-18	8.45E-15	1.48	12.14	6q23
26	238022_at		-5.45	3.57E-12	7.83E-10	-1.75	-12.03	
27	210982_s_at	HLA-DRA	6.63	4.86E-18	7.33E-15	1.43	11.89	6p21.3
28	34210_at	CDW52	32.32	2.83E-16	2.50E-13	1.56	11.88	1p36
29	224839_s_at	GPT2	-9.22	1.05E-10	1.48E-08	-2.02	-11.85	16q12.1
30	200654_at	P4HB	-1.95	1.16E-14	6.63E-12	-1.49	-11.66	17q25
31	241742_at	PRAM-1	9.22	6.13E-16	5.07E-13	1.48	11.49	19p13.2
32	204362_at	SCAP2	10.45	1.78E-16	1.83E-13	1.41	11.43	7p21-p15
33	208891_at	DUSP6	6.45	2.17E-17	2.79E-14	1.36	11.38	12q22-q23
34	241239_at		6.33	2.46E-16	2.34E-13	1.40	11.35	
35	204150_at	STAB1	-13.65	6.04E-10	6.74E-08	-2.22	-11.28	3p21.31
36	236554_x_at	EVER2	3.47	3.18E-17	3.71E-14	1.35	11.28	17q25.3
37	204440_at	CD83	5.53	4.71E-17	5.26E-14	1.35	11.24	6p23
38	208894_at	HLA-DRA	6.44	5.21E-17	5.58E-14	1.34	11.17	6p21.3

39	204425_at	ARHGAP4	18.14	2.90E-15	2.13E-12	1.47	11.16	Xq28
40	217716_s_at	SEC61A1	-1.99	1.21E-11	2.34E-09	-1.59	-11.11	3q21.3
41	201522_x_at	SNRPN	3.51	7.84E-13	2.16E-10	1.48	11.10	15q12
42	208613_s_at	FLNB	8.30	3.23E-15	2.30E-12	1.39	10.92	3p14.3
43	200931_s_at	VCL	3.50	2.27E-16	2.24E-13	1.30	10.86	10q22.1-q23
44	221865_at	DKFZp547P234	3.33	2.66E-16	2.44E-13	1.30	10.82	9q33.1
45	226733_at	PFKFB2	5.78	1.39E-15	1.12E-12	1.28	10.58	1q31
46	201034_at	ADD3	4.15	5.43E-16	4.65E-13	1.26	10.57	10q24.2-q24.3
47	225639_at	SCAP2	9.79	2.74E-15	2.07E-12	1.29	10.54	7p21-p15
48	208892_s_at	DUSP6	6.48	1.67E-15	1.30E-12	1.26	10.47	12q22-q23
49	202917_s_at	S100A8	3.17	9.40E-14	3.66E-11	1.31	10.46	1q21
50	238365_s_at		-5.11	1.53E-10	2.03E-08	-1.53	-10.33	

2.5 AML_MLL versus AML_inv(3)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	204082_at	PBX3	8.60	2.88E-12	2.35E-08	1.63	10.50	9q33-q34
2	226789_at		3.28	1.48E-13	1.81E-09	1.47	10.39	
3	214651_s_at	HOXA9	4.67	9.43E-14	1.81E-09	1.45	10.29	7p15-p14
4	235753_at		4.92	3.97E-12	2.43E-08	1.42	9.76	
5	228083_at	CACNA2D4	11.16	1.43E-11	5.83E-08	1.46	9.66	12p13.33
6	214643_x_at	BIN1	-4.56	2.50E-09	1.64E-06	-1.59	-9.58	2q14
7	209905_at	HOXA9	7.79	3.17E-11	1.11E-07	1.34	9.13	7p15-p14
8	202054_s_at	ALDH3A2	5.02	6.40E-12	3.14E-08	1.27	9.05	17p11.2
9	208116_s_at	MAN1A1	-4.86	2.19E-08	6.38E-06	-1.59	-8.95	6q22
10	236398_s_at		5.77	7.08E-11	1.58E-07	1.31	8.88	
11	201829_at	NET1	-3.59	3.90E-08	9.18E-06	-1.61	-8.81	10p15
12	203733_at	MYLE	2.69	6.75E-11	1.58E-07	1.23	8.59	16p13.2
13	212318_at	TRN-SR	2.53	8.52E-11	1.67E-07	1.23	8.55	7q32.2
14	233955_x_at	HSPC195	-4.61	1.78E-08	5.60E-06	-1.41	-8.54	5q31.3
15	213893_x_at	PMS2L5	2.24	3.81E-11	1.17E-07	1.19	8.49	7q11-q22
16	208702_x_at	APLP2	2.83	4.39E-11	1.19E-07	1.19	8.45	11q24
17	231431_s_at		-2.62	7.32E-08	1.39E-05	-1.54	-8.45	
18	202605_at	GUSB	3.28	9.55E-11	1.67E-07	1.20	8.44	7q21.11
19	210006_at	DKFZP564O243	2.17	1.66E-10	2.71E-07	1.21	8.40	3p21.1
20	210201_x_at	BIN1	-2.98	1.82E-08	5.64E-06	-1.35	-8.34	2q14
21	214439_x_at	BIN1	-3.31	1.27E-08	4.55E-06	-1.31	-8.27	2q14
22	212782_x_at	POLR2J	2.38	3.41E-10	4.29E-07	1.18	8.24	7q11.2
23	200602_at	APP	-10.57	8.51E-08	1.58E-05	-1.47	-8.24	21q21.3
24	214875_x_at	APLP2	2.72	9.39E-11	1.67E-07	1.15	8.23	11q24
25	219551_at	TRAITS	3.35	3.68E-10	4.29E-07	1.19	8.19	3q13.33
26	206847_s_at	HOXA7	2.98	2.37E-10	3.23E-07	1.16	8.15	7p15-p14
27	218217_at	RISC	4.10	1.13E-09	9.89E-07	1.23	8.14	17q23.1
28	223703_at	CDA017	3.49	1.23E-09	1.00E-06	1.22	8.09	10q23.1
29	201186_at	LRPAP1	3.21	7.48E-10	7.89E-07	1.18	8.07	4p16.3

30	201105_at	LGALS1	2.91	1.88E-10	2.88E-07	1.12	8.00	22q13.1
31	203725_at	GADD45A	-3.08	1.71E-09	1.27E-06	-1.16	-7.99	1p31.2-p31.1
32	214430_at	GLA	2.03	2.27E-10	3.23E-07	1.12	7.97	Xq22
33	206440_at	LIN7A	8.55	1.13E-09	9.89E-07	1.17	7.97	12q21
34	211709_s_at	SCGF	4.44	4.41E-10	4.91E-07	1.11	7.86	19q13.3
35	219033_at	FLJ21308	3.62	1.20E-09	1.00E-06	1.14	7.85	5q11.1
36	219126_at	XAP135	1.85	3.53E-10	4.29E-07	1.10	7.84	6q27
37	208967_s_at	AK2	3.68	3.22E-09	1.84E-06	1.20	7.83	1p34
38	212174_at	AK2	3.63	1.63E-09	1.24E-06	1.15	7.83	1p34
39	202053_s_at	ALDH3A2	2.61	9.28E-10	8.75E-07	1.11	7.78	17p11.2
40	202961_s_at	ATP5J2	2.16	8.60E-10	8.43E-07	1.10	7.77	7q22.1
41	201830_s_at	NET1	-5.62	3.42E-07	3.90E-05	-1.47	-7.75	10p15
42	231300_at	LOC90835	4.14	2.74E-09	1.68E-06	1.15	7.74	16p11.2
43	204951_at	ARHH	-3.59	3.51E-08	8.51E-06	-1.21	-7.71	4p13
44	211404_s_at	APLP2	2.23	1.44E-09	1.14E-06	1.09	7.65	11q24
45	219991_at	SLC2A9	2.29	2.55E-09	1.64E-06	1.12	7.64	4p16-p15.3
46	223328_at	MGC3195	2.12	7.73E-10	7.89E-07	1.07	7.61	7q22.1
47	213908_at		3.56	4.03E-09	2.10E-06	1.12	7.58	
48	228652_at	FLJ38288	-2.21	6.80E-08	1.32E-05	-1.21	-7.58	19q13.43
49	214953_s_at	APP	-5.50	1.23E-07	1.99E-05	-1.23	-7.52	21q21.3
50	202931_x_at	BIN1	-3.09	1.11E-07	1.89E-05	-1.21	-7.50	2q14

2.6 AML_MLL versus AML_komplext

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	201377_at	NICE-4	-2.72	3.69E-15	2.46E-11	-1.51	-11.56	1q21.3
2	201105_at	LGALS1	4.52	6.07E-14	2.57E-10	1.36	10.55	22q13.1
3	200608_s_at	RAD21	-1.86	3.88E-15	2.46E-11	-1.28	-10.40	8q24
4	228083_at	CACNA2D4	11.81	1.68E-11	9.93E-09	1.53	9.94	12p13.33
5	201830_s_at	NET1	-5.21	6.70E-12	6.55E-09	-1.37	-9.77	10p15
6	201225_s_at	SRRM1	-1.72	1.39E-13	4.42E-10	-1.18	-9.52	1p36.11
7	208886_at	H1F0	-7.16	2.03E-11	9.93E-09	-1.32	-9.40	22q13.1
8	214700_x_at	DKFZP434D193	-3.12	1.37E-11	9.65E-09	-1.27	-9.33	2q23.3
9	209022_at	STAG2	-1.98	3.31E-12	5.25E-09	-1.17	-9.17	Xq25
10	218041_x_at	SLC38A2	-1.84	3.42E-13	8.70E-10	-1.12	-9.13	12q
11	203544_s_at	STAM	-4.39	3.49E-11	1.48E-08	-1.26	-9.11	10p14-p13
12	218823_s_at	FLJ20038	-2.77	3.12E-11	1.41E-08	-1.25	-9.09	8p21.1
13	201196_s_at	AMD1	-1.93	1.72E-12	3.49E-09	-1.14	-9.09	6q21-q22
14	201560_at	CLIC4	-4.16	4.61E-12	5.33E-09	-1.16	-9.07	1p36.11
15	202746_at	ITM2A	-10.44	1.47E-10	3.83E-08	-1.28	-8.85	Xq13.3-Xq21.2
16	209705_at		-2.03	1.78E-11	9.93E-09	-1.14	-8.80	
17	205788_s_at	KIAA0663	-1.79	1.87E-11	9.93E-09	-1.14	-8.78	1q32.1
18	203519_s_at	UPF2	-2.09	1.91E-11	9.93E-09	-1.13	-8.75	10p14-p13
19	222902_s_at	FLJ21144	-1.92	1.92E-12	3.49E-09	-1.08	-8.75	1p34.1
20	233168_s_at	IMAGE3510317	-1.73	4.52E-12	5.33E-09	-1.09	-8.75	22q13.33

21	209362_at	SURB7	-2.15	1.91E-11	9.93E-09	-1.11	-8.67	12p11.23
22	204082_at	PBX3	4.49	5.32E-11	2.05E-08	1.14	8.66	9q33-q34
23	201585_s_at	SFPQ	-1.91	9.60E-12	8.21E-09	-1.09	-8.65	1p34.3
24	200997_at	RBM4	-1.92	1.18E-11	8.79E-09	-1.09	-8.64	11q13
25	201829_at	NET1	-3.30	1.95E-10	4.21E-08	-1.21	-8.62	10p15
26	239071_at		-1.83	3.72E-12	5.25E-09	-1.04	-8.51	
27	203725_at	GADD45A	-4.33	6.08E-11	2.21E-08	-1.11	-8.51	1p31.2-p31.1
28	211137_s_at	ATP2C1	-3.12	4.82E-10	7.28E-08	-1.26	-8.50	3q21-q24
29	202747_s_at	ITM2A	-10.27	3.18E-10	5.61E-08	-1.20	-8.49	Xq13.3-Xq21.2
30	201166_s_at	PUM1	-1.86	3.89E-11	1.60E-08	-1.09	-8.49	1p35.2
31	212232_at	FNBP4	-1.77	1.15E-11	8.79E-09	-1.05	-8.43	11p11.12
32	200086_s_at - HG-U133B	COX4I1	1.64	5.17E-12	5.47E-09	1.03	8.43	16q22-qter
33	223318_s_at	MGC10974	3.61	2.44E-10	4.77E-08	1.14	8.38	19p13.3
34	212463_at		-4.10	1.52E-10	3.83E-08	-1.11	-8.35	
35	213549_at	PRO2730	-4.66	6.44E-10	8.52E-08	-1.21	-8.33	3p21.31
36	201358_s_at	COPB	-1.65	1.96E-11	9.93E-09	-1.04	-8.33	11p15.2
37	212031_at	S164	-2.00	1.55E-11	9.93E-09	-1.03	-8.32	14q24.3
38	228974_at		-4.54	1.70E-10	4.01E-08	-1.10	-8.31	
39	205849_s_at	UQCRB	1.52	9.70E-12	8.21E-09	1.02	8.31	8q22
40	201061_s_at	STOM	-3.25	2.69E-10	5.17E-08	-1.12	-8.31	9q34.1
41	205639_at	AOAH	3.94	2.96E-10	5.43E-08	1.12	8.29	7p14-p12
42	218331_s_at	FLJ20360	-2.05	6.54E-11	2.31E-08	-1.06	-8.28	10p15.1
43	223592_s_at	MGC13061	2.62	2.99E-10	5.43E-08	1.12	8.28	17q11.2
44	217887_s_at	EPS15	-2.10	5.29E-11	2.05E-08	-1.05	-8.26	1p32
45	200985_s_at	CD59	-4.95	1.95E-10	4.21E-08	-1.09	-8.25	11p13
46	214439_x_at	BIN1	-3.72	2.41E-10	4.77E-08	-1.09	-8.21	2q14
47	200071_at - HG-U133A	SPF30	-1.89	7.53E-11	2.52E-08	-1.04	-8.19	10q23
48	202413_s_at	USP1	-1.73	3.43E-11	1.48E-08	-1.01	-8.16	1p32.1-p31.3
49	218846_at	CRSP3	-2.57	3.67E-10	6.13E-08	-1.09	-8.15	6q22.33-q24.1
50	202659_at	PSMB10	3.04	1.05E-10	3.27E-08	1.04	8.15	16q22.1

2.7 AML_MLL versus AML_t(15;17)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	221004_s_at	ITM2C	-9.69	6.96E-15	2.78E-11	-2.63	-16.45	2q37
2	38487_at	STAB1	-16.22	3.38E-13	4.51E-10	-2.90	-16.13	3p21.31
3	203948_s_at	MPO	-6.32	8.76E-21	2.10E-16	-2.19	-15.83	17q23.1
4	214651_s_at	HOXA9	237.17	2.30E-16	1.84E-12	2.66	15.41	7p15-p14
5	205624_at	CPA3	-36.02	6.17E-12	3.79E-09	-3.01	-14.75	3q21-q25
6	212953_x_at	CALR	-3.21	2.50E-14	6.66E-11	-2.22	-14.41	19p13.3-p13.2
7	214450_at	CTSW	-6.11	7.04E-14	1.41E-10	-2.21	-14.15	11q13.1
8	203949_at	MPO	-4.43	9.42E-19	1.13E-14	-1.91	-13.87	17q23.1

9	200953_s_at	CCND2	-6.10	3.06E-12	2.45E-09	-2.26	-13.42	12p13
10	213147_at	HOXA10	23.93	1.62E-14	4.85E-11	2.12	13.06	7p15-p14
11	238022_at		-5.73	4.14E-12	3.00E-09	-1.96	-12.30	
12	235753_at		16.83	1.12E-13	1.79E-10	2.04	12.26	
13	233072_at	KIAA1857	-11.75	7.57E-11	2.44E-08	-2.24	-12.25	9q34
14	205771_s_at	AKAP7	10.25	3.35E-14	8.02E-11	1.82	12.10	6q23
15	206871_at	ELA2	-3.69	4.90E-16	2.94E-12	-1.64	-11.89	19p13.3
16	206847_s_at	HOXA7	9.48	6.90E-14	1.41E-10	1.80	11.89	7p15-p14
17	209448_at	HTATIP2	10.38	2.48E-13	3.64E-10	1.79	11.54	11p15.1
18	204150_at	STAB1	-19.25	3.63E-10	8.30E-08	-2.23	-11.50	3p21.31
19	213587_s_at	LOC155066	7.64	6.58E-13	7.88E-10	1.79	11.29	7q36.1
20	205663_at	PCBP3	-3.93	3.63E-11	1.36E-08	-1.79	-11.19	21q22.3
21	201522_x_at	SNRPN	4.63	2.51E-15	1.20E-11	1.54	11.19	15q12
22	212509_s_at		-6.33	1.53E-10	4.37E-08	-1.87	-11.08	
23	209905_at	HOXA9	720.22	1.83E-12	1.75E-09	1.92	11.06	7p15-p14
24	205349_at	GNA15	-4.14	1.47E-12	1.53E-09	-1.62	-11.03	19p13.3
25	200951_s_at	CCND2	-6.76	2.21E-10	5.88E-08	-1.88	-10.98	12p13
26	206761_at	TACTILE	-28.74	1.21E-09	2.02E-07	-2.29	-10.90	3q13.13
27	201029_s_at	CD99	-2.16	1.08E-14	3.69E-11	-1.48	-10.74	Xp22.32
28	217848_s_at	PP	3.89	1.09E-13	1.79E-10	1.49	10.59	10q11.1-q24
29	225532_at	LOC91768	-5.64	9.02E-10	1.64E-07	-1.92	-10.59	18q11.1
30	200952_s_at	CCND2	-4.07	2.77E-10	6.83E-08	-1.76	-10.57	12p13
31	204425_at	ARHGAP4	15.58	4.11E-12	3.00E-09	1.65	10.49	Xq28
32	204082_at	PBX3	8.50	2.90E-12	2.40E-09	1.61	10.47	9q33-q34
33	231736_x_at	MGST1	-2.80	2.58E-13	3.64E-10	-1.46	-10.42	12p12.3-p12.1
34	210788_s_at	retSDR4	-2.38	2.11E-11	9.75E-09	-1.57	-10.41	14q22.3
35	224918_x_at	MGST1	-2.62	9.12E-14	1.68E-10	-1.42	-10.30	12p12.3-p12.1
36	201596_x_at	KRT18	-8.14	5.16E-10	1.08E-07	-1.69	-10.20	12q13
37	213150_at	HOXA10	45.69	1.41E-11	7.20E-09	1.71	10.17	7p15-p14
38	218404_at	SNX10	6.77	5.71E-12	3.60E-09	1.53	10.09	7p15.2
39	225386_s_at	LOC92906	34.47	1.65E-11	8.20E-09	1.66	10.08	2p22.2
40	211474_s_at	SERPINB6	4.55	2.77E-12	2.40E-09	1.47	10.04	6p25
41	221253_s_at	MGC3178	-2.99	2.44E-10	6.44E-08	-1.59	-10.03	6p24.3
42	228083_at	CACNA2D4	11.77	1.68E-11	8.20E-09	1.57	9.93	12p13.33
43	213571_s_at	EIF4EL3	2.54	6.08E-13	7.67E-10	1.37	9.84	2q37.1
44	208852_s_at	CANX	-2.26	6.45E-11	2.18E-08	-1.46	-9.78	5q35
45	227999_at	LOC170394	3.11	7.06E-13	8.06E-10	1.36	9.76	10q26.3
46	217716_s_at	SEC61A1	-1.93	1.04E-11	5.68E-09	-1.40	-9.72	3q21.3
47	202265_at	BMI1	4.29	8.23E-12	4.70E-09	1.43	9.71	10p11.23
48	217853_at	TEM6	6.43	1.19E-11	6.31E-09	1.43	9.66	7p15.1
49	223663_at	FLJ37970	6.99	2.35E-12	2.17E-09	1.37	9.66	11q12.3
50	228263_at	GRASP	-2.66	3.59E-12	2.77E-09	-1.36	-9.63	12q13.13

2.8 AML_inv(3) versus AML_komplext

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	222229_x_at		1.59	1.43E-12	2.58E-08	1.49	10.36	
2	206781_at	DNAJC4	2.26	7.27E-11	4.54E-07	1.37	9.35	11q13
3	208730_x_at	RAB2	2.22	1.23E-09	1.71E-06	1.38	9.00	8q12.1
4	200093_s_at - HG-U133B	HINT1	1.88	6.67E-10	1.71E-06	1.21	8.35	5q31.2
5	213682_at	NUP50	-1.96	7.52E-11	4.54E-07	-1.14	-8.23	22q13.31
6	227708_at	EEF1A1	2.34	1.67E-08	8.16E-06	1.30	8.20	6q14.1
7	208826_x_at	HINT1	1.52	5.20E-10	1.64E-06	1.14	8.05	5q31.2
8	201202_at	PCNA	-2.84	2.31E-10	1.05E-06	-1.10	-7.93	20pter-p12
9	209122_at	ADFP	-4.15	1.08E-09	1.71E-06	-1.12	-7.82	9p21.3
10	200700_s_at	KDELR2	-2.80	1.13E-09	1.71E-06	-1.09	-7.67	7p22.2
11	201377_at	NICE-4	-1.90	5.46E-10	1.64E-06	-1.06	-7.67	1q21.3
12	203538_at	CAMLG	2.07	4.91E-08	1.51E-05	1.20	7.65	5q23
13	205436_s_at	H2AFX	-3.79	2.79E-09	2.71E-06	-1.12	-7.64	11q23.2-q23.3
14	218883_s_at	FLJ23468	-2.56	8.92E-10	1.71E-06	-1.07	-7.63	4q35.1
15	200094_s_at - HG-U133A	EEF2	1.41	4.93E-09	3.72E-06	1.09	7.56	19pter-q12
16	201663_s_at	SMC4L1	-2.49	1.36E-09	1.76E-06	-1.06	-7.55	3q26.1
17	201386_s_at	DDX15	-1.79	9.01E-10	1.71E-06	-1.05	-7.53	4p15.3
18	222047_s_at	ARS2	-1.55	1.08E-09	1.71E-06	-1.04	-7.50	7q21
19	212491_s_at	DNAJC8	-1.75	2.35E-09	2.61E-06	-1.05	-7.47	1p35.2
20	206550_s_at	NUP155	-2.08	2.18E-09	2.61E-06	-1.04	-7.40	5p13.1
21	203421_at	PIG11	-6.24	1.66E-08	8.16E-06	-1.14	-7.30	11p11.2
22	212031_at	S164	-1.92	2.84E-09	2.71E-06	-1.02	-7.28	14q24.3
23	213008_at	FLJ10719	-2.96	2.45E-09	2.61E-06	-1.01	-7.25	15q25-q26
24	202580_x_at	FOXM1	-3.95	7.57E-09	4.72E-06	-1.05	-7.25	12p13
25	218115_at	ASF1B	-2.62	4.20E-09	3.55E-06	-1.02	-7.24	19p13.12
26	213088_s_at	DNAJC9	-2.44	7.48E-09	4.72E-06	-1.03	-7.18	10q22.2
27	213292_s_at	SNX13	-2.17	6.26E-09	4.35E-06	-1.01	-7.16	7p21.1
28	204695_at	CDC25A	-4.38	1.11E-08	6.26E-06	-1.03	-7.14	3p21
29	218585_s_at	RAMP	-3.20	1.41E-08	7.48E-06	-1.04	-7.12	
30	208715_at	LOC54499	-2.21	4.16E-09	3.55E-06	-0.99	-7.11	1q22-q25
31	201457_x_at	BUB3	-1.73	4.55E-09	3.57E-06	-0.99	-7.10	10q26
32	222680_s_at	RAMP	-2.06	4.32E-09	3.55E-06	-0.98	-7.10	
33	211950_at	RBAF600	-2.14	6.18E-09	4.35E-06	-0.99	-7.08	1p36.13
34	223157_at	MGC3232	2.00	4.48E-07	5.23E-05	1.18	7.07	4q12
35	215123_at		-3.06	7.02E-09	4.70E-06	-0.97	-6.98	
36	227165_at	C13orf3	-2.41	1.84E-08	8.51E-06	-1.01	-6.98	13q11
37	218350_s_at	GMNN	-2.41	1.04E-08	6.07E-06	-0.97	-6.93	6p22.1
38	202954_at	UBE2C	-3.17	3.02E-08	1.21E-05	-1.02	-6.91	20q13.11
39	232247_at	FLJ14855	-2.01	8.55E-09	5.15E-06	-0.96	-6.91	3p21.31
40	214141_x_at	SFRS7	-1.77	1.72E-08	8.17E-06	-0.98	-6.90	2p22.1
41	201680_x_at	ARS2	-1.59	1.17E-08	6.43E-06	-0.95	-6.82	7q21
42	202413_s_at	USP1	-1.82	3.54E-08	1.31E-05	-0.97	-6.82	1p32.1-p31.3
43	209619_at	CD74	2.00	1.60E-07	2.89E-05	1.03	6.82	5q32
44	200094_s_at - HG-U133B	EEF2	1.39	4.08E-08	1.44E-05	0.98	6.81	19pter-q12

45	226123_at	LOC286180	-3.56	2.20E-08	9.47E-06	-0.96	-6.80	8q12.1
46	204709_s_at	KIF23	-4.17	6.32E-08	1.77E-05	-1.03	-6.80	15q22.31
47	210140_at	CST7	-4.76	5.60E-08	1.66E-05	-1.01	-6.78	20p11.21
48	210178_x_at	FUSIP1	-1.97	1.54E-08	7.94E-06	-0.94	-6.77	1p36.11
49	227056_at		3.40	1.85E-06	1.23E-04	1.20	6.72	
50	204023_at	RFC4	-2.23	1.88E-08	8.51E-06	-0.93	-6.70	3q27

2.9 AML_inv(3) versus AML_t(15;17)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	203948_s_at	MPO	-9.22	7.85E-20	8.48E-16	-3.33	-20.18	17q23.1
2	203949_at	MPO	-5.92	7.32E-21	1.58E-16	-3.19	-19.69	17q23.1
3	205382_s_at	DF	-12.00	3.95E-15	1.07E-11	-3.44	-18.83	19p13.3
4	212953_x_at	CALR	-4.97	5.32E-16	2.30E-12	-2.76	-16.36	19p13.3-p13.2
5	200654_at	P4HB	-3.54	5.30E-18	3.81E-14	-2.62	-16.13	17q25
6	224918_x_at	MGST1	-5.40	5.25E-17	2.83E-13	-2.49	-15.29	12p12.3-p12.1
7	231736_x_at	MGST1	-6.11	7.03E-16	2.53E-12	-2.51	-15.14	12p12.3-p12.1
8	214450_at	CTSW	-6.80	4.70E-14	1.02E-10	-2.44	-14.29	11q13.1
9	205624_at	CPA3	-18.38	6.13E-12	5.51E-09	-2.76	-14.18	3q21-q25
10	206871_at	ELA2	-5.26	1.18E-15	3.64E-12	-2.20	-13.53	19p13.3
11	211990_at	HLA-DPA1	12.46	4.97E-11	2.98E-08	2.67	13.52	6p21.3
12	38487_at	STAB1	-5.47	4.81E-13	6.92E-10	-2.24	-13.06	3p21.31
13	217716_s_at	SEC61A1	-2.52	1.00E-13	1.65E-10	-2.15	-12.88	3q21.3
14	214575_s_at	AZU1	-8.67	1.00E-13	1.65E-10	-2.12	-12.73	19p13.3
15	238022_at		-7.63	7.53E-13	9.07E-10	-2.12	-12.49	
16	208852_s_at	CANX	-3.04	3.58E-12	3.68E-09	-2.18	-12.48	5q35
17	221739_at	IL27w	-2.20	1.28E-14	3.06E-11	-2.02	-12.47	19p13.3
18	208689_s_at	RPN2	-2.59	1.07E-13	1.65E-10	-2.02	-12.26	20q12-q13.1
19	221004_s_at	ITM2C	-4.37	5.63E-14	1.11E-10	-1.99	-12.16	2q37
20	233072_at	KIAA1857	-9.87	1.26E-10	6.35E-08	-2.39	-12.10	9q34
21	210788_s_at	retSDR4	-2.78	4.14E-12	4.06E-09	-2.00	-11.71	14q22.3
22	206914_at	CRTAM	6.73	2.22E-11	1.60E-08	2.03	11.62	11q22-q23
23	211709_s_at	SCGF	-5.57	6.43E-13	8.68E-10	-1.91	-11.55	19q13.3
24	213716_s_at	SECTM1	10.56	1.74E-09	5.54E-07	2.25	11.11	17q25
25	227353_at	EVER2	5.13	2.92E-10	1.24E-07	2.00	11.00	17q25.3
26	209021_x_at	KIAA0652	-5.31	1.35E-11	1.12E-08	-1.84	-10.90	11p11.12
27	214797_s_at	PCTK3	5.81	2.43E-10	1.05E-07	1.95	10.87	1q31-q32
28	208730_x_at	RAB2	2.63	4.23E-10	1.72E-07	1.98	10.86	8q12.1
29	202487_s_at	H2AV	-2.35	7.56E-13	9.07E-10	-1.76	-10.82	7p13
30	203675_at	NUCB2	-3.45	1.59E-11	1.27E-08	-1.83	-10.81	11p15.1-p14
31	217225_x_at	LOC283820	-2.26	2.10E-12	2.26E-09	-1.77	-10.77	16p13.13
32	200652_at	SSR2	-1.99	1.05E-12	1.19E-09	-1.73	-10.68	1q21-q23
33	209215_at	TETRAN	-3.46	4.99E-12	4.68E-09	-1.75	-10.63	4p16.3
34	229168_at	DKFZp434K0621	-4.90	5.86E-10	2.30E-07	-1.95	-10.53	5q35.3

35 209619_at	CD74	4.55	1.98E-11	1.47E-08	1.72	10.36	5q32
36 221253_s_at	MGC3178	-3.26	1.04E-10	5.78E-08	-1.78	-10.33	6p24.3
37 210140_at	CST7	-8.32	1.51E-09	5.06E-07	-1.98	-10.31	20p11.21
38 224839_s_at	GPT2	-6.24	6.83E-11	3.88E-08	-1.74	-10.23	16q12.1
39 217770_at	PIGT	-2.32	1.69E-11	1.30E-08	-1.68	-10.17	20q12-q13.12
40 205614_x_at	MST1	-9.35	3.11E-09	8.56E-07	-2.03	-10.12	3p21
41 209732_at	CLECSF2	29.15	1.41E-08	2.74E-06	2.22	10.02	12p13-p12
42 201004_at	SSR4	-2.56	2.78E-11	1.82E-08	-1.64	-9.95	Xq28
43 204897_at	PTGER4	5.27	1.51E-10	7.41E-08	1.68	9.90	5p13.1
44 201029_s_at	CD99	-1.81	1.13E-11	9.73E-09	-1.61	-9.89	Xp22.32
45 241696_at		3.13	3.64E-11	2.25E-08	1.62	9.81	
46 214789_x_at	SRP46	4.12	8.67E-10	3.28E-07	1.71	9.76	11q22
47 201825_s_at	CGI-49	-3.27	2.66E-11	1.79E-08	-1.57	-9.61	1q44
48 204150_at	STAB1	-5.48	2.26E-09	6.96E-07	-1.74	-9.57	3p21.31
49 241383_at		-4.21	2.75E-09	7.92E-07	-1.75	-9.55	
50 200068_s_at - HG-U133B	CANX	-1.65	2.98E-11	1.89E-08	-1.55	-9.52	5q35

2.10 AML_komplext versus AML_t(15;17)

#	affy id	HUGO name	fc	p	q	stn	t	Map Location
1	205382_s_at	DF	-7.84	1.62E-15	2.79E-12	-2.74	-17.32	19p13.3
2	212953_x_at	CALR	-3.21	1.30E-13	9.18E-11	-2.45	-15.03	19p13.3-p13.2
3	203948_s_at	MPO	-4.01	3.68E-19	4.69E-15	-2.02	-14.64	17q23.1
4	214450_at	CTSW	-6.67	6.70E-14	6.09E-11	-2.28	-14.52	11q13.1
5	38487_at	STAB1	-5.91	5.67E-13	2.67E-10	-2.18	-13.64	3p21.31
6	216032_s_at	SDBCAG84	-3.37	2.16E-14	2.29E-11	-2.03	-13.59	20pter-q12
7	208826_x_at	HINT1	-1.69	7.49E-18	4.77E-14	-1.76	-12.96	5q31.2
8	238022_at		-7.84	7.82E-13	3.55E-10	-1.99	-12.81	
9	213147_at	HOXA10	11.01	4.54E-15	5.75E-12	1.91	12.80	7p15-p14
10	200931_s_at	VCL	4.91	6.72E-16	1.71E-12	1.82	12.74	10q22.1-q23
11	209732_at	CLECSF2	35.32	4.46E-14	4.37E-11	2.04	12.46	12p13-p12
12	200654_at	P4HB	-2.34	2.10E-16	8.89E-13	-1.70	-12.36	17q25
13	207721_x_at	HINT1	-1.89	6.21E-16	1.71E-12	-1.57	-11.54	5q31.2
14	200047_s_at - HG-U133A	YY1	2.32	1.07E-15	2.27E-12	1.55	11.37	14q
15	203949_at	MPO	-2.48	1.75E-15	2.79E-12	-1.53	-11.23	17q23.1
16	200093_s_at - HG-U133B	HINT1	-1.89	2.93E-15	4.15E-12	-1.50	-11.06	5q31.2
17	201923_at	PRDX4	8.38	3.10E-13	1.80E-10	1.63	11.02	Xp22.13
18	204897_at	PTGER4	5.03	4.97E-15	5.75E-12	1.48	10.91	5p13.1
19	217225_x_at	LOC283820	-2.07	6.98E-12	1.85E-09	-1.59	-10.73	16p13.13
20	227353_at	EVER2	4.55	1.06E-13	7.94E-11	1.51	10.69	17q25.3
21	206847_s_at	HOXA7	4.94	9.60E-14	7.94E-11	1.47	10.53	7p15-p14
22	227999_at	LOC170394	3.30	1.56E-13	1.04E-10	1.41	10.21	10q26.3
23	202600_s_at	NRIP1	12.57	3.27E-12	9.68E-10	1.52	10.19	21q11.2

24	207375_s_at	IL15RA	5.82	1.33E-12	5.36E-10	1.46	10.16	10p15-p14
25	214789_x_at	SRP46	3.86	1.77E-13	1.13E-10	1.40	10.14	11q22
26	221004_s_at	ITM2C	-3.41	2.27E-13	1.38E-10	-1.40	-10.14	2q37
27	204150_at	STAB1	-6.71	1.26E-09	8.02E-08	-1.73	-10.06	3p21.31
28	200934_at	DEK	2.41	1.06E-13	7.94E-11	1.36	10.01	6p23
29	208892_s_at	DUSP6	6.46	1.35E-12	5.36E-10	1.39	9.84	12q22-q23
30	202413_s_at	USP1	2.49	4.61E-13	2.37E-10	1.35	9.84	1p32.1-p31.3
31	217848_s_at	PP	3.96	1.63E-12	6.11E-10	1.38	9.78	10q11.1-q24
32	208891_at	DUSP6	6.82	9.06E-13	3.98E-10	1.36	9.77	12q22-q23
33	220798_x_at	FLJ11535	-3.66	2.63E-11	5.28E-09	-1.42	-9.75	19p13.3
34	224473_x_at	KIAA1813	2.33	9.97E-13	4.23E-10	1.36	9.75	10q24
35	225547_at		1.73	3.36E-13	1.86E-10	1.33	9.75	
36	200008_s_at - HG-U133A	GDI2	-2.39	1.53E-11	3.41E-09	-1.40	-9.74	10p15
37	238949_at	FLJ31951	8.00	5.50E-12	1.49E-09	1.41	9.71	5q33.3
38	203535_at	S100A9	7.92	3.22E-12	9.68E-10	1.38	9.68	1q21
39	210788_s_at	retSDR4	-2.19	8.24E-11	1.17E-08	-1.44	-9.67	14q22.3
40	226460_at	KIAA1450	3.63	1.79E-12	6.33E-10	1.35	9.66	4q32.1
41	200093_s_at - HG-U133A	HINT1	-1.69	5.55E-13	2.67E-10	-1.32	-9.63	5q31.2
42	225172_at	CRAMP1L	2.61	4.65E-13	2.37E-10	1.31	9.60	16p13.3
43	229693_at		-2.78	1.07E-10	1.42E-08	-1.42	-9.56	
44	203302_at	DCK	4.08	4.56E-12	1.30E-09	1.33	9.44	4q13.3-q21.1
45	200656_s_at	P4HB	-4.16	1.53E-09	9.31E-08	-1.51	-9.39	17q25
46	205033_s_at	DEFA1	5.34	2.50E-12	8.36E-10	1.30	9.37	8p23.2-p23.1
47	227308_x_at	SCYL1	4.60	1.47E-11	3.34E-09	1.35	9.36	
48	205663_at	PCBP3	-3.06	1.14E-10	1.44E-08	-1.37	-9.35	21q22.3
49	202599_s_at	NRIP1	8.20	2.13E-11	4.38E-09	1.36	9.31	21q11.2
50	221087_s_at	APOL3	3.50	4.58E-12	1.30E-09	1.29	9.29	22q13.1

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(74) Common Representative: **ROCHE DIAGNOSTICS GMBH**; c/o Burger, Alexander, Patent Department (TR-E), Postfach 11 52, 82372 Penzberg (DE).

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(54) Title: METHOD FOR DISTINGUISHING CBF-POSITIVE AML SUBTYPES FROM CBF-NEGATIVE AML SUBTYPES

(57) Abstract: Disclosed is a method for distinguishing CBF-positive AML subtypes from CBF-negative AML subtypes in a sample by determining the expression level of markers, as well as a diagnostic kit and an apparatus containing the markers.

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INTERNATIONAL SEARCH REPORT

International Application No
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Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/039443 A (DEUTSCHES KREBSFORSCH ;HAFERLACH TORSTEN (DE); EILS ROLAND (DE); K) 15 May 2003 (2003-05-15) the whole document in particular Examples 4, 6 and 7 ----- -/--	1-27

[X] Further documents are listed in the continuation of box C.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2005	09. 06. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Thumb, W

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHOCH CLAUDIA ET AL: "Acute myeloid leukemias with reciprocal rearrangements can be distinguished by specific gene expression profiles" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 99, no. 15, 23 July 2002 (2002-07-23), pages 10008-10013, XP002215484 ISSN: 0027-8424 the whole document in particular tables 1 and 2	1-27
Y	KOHLMANN A ET AL: "MOLECULAR CHARACTERIZATION OF ACUTE LEUKEMIAS BY USE OF MICROARRAY TECHNOLOGY" GENES, CHROMOSOMES & CANCER, XX, XX, vol. 37, no. 4, August 2003 (2003-08), pages 396-405, XP008025253 the whole document in particular table 2	1-27
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2002 (2002-11-16), KOHLMANN ALEXANDER ET AL: "A Gene Expression Study of 59 Acute Myeloid Leukemia (AML) Patients with Recurrent Cytogenetic Abnormalities." XP002269490 Database accession no. PREV200300335805 abstract & BLOOD, vol. 100, no. 11, 16 November 2002 (2002-11-16), page Abstract No. 1205, 44th Annual Meeting of the American Society of Hematology;Philadelphia, PA, USA; December 06-10, 2002 ISSN: 0006-4971	1-27
Y	HAFERLACH T ET AL: "The Diagnosis of 14 Specific Subtypes of Leukemia Is Possible Based on Gene Expression Profiles: A Study on 263 Patients with AML, ALL, CML, or CLL" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 100, no. 11, 16 November 2002 (2002-11-16), page 139A, XP002263227 ISSN: 0006-4971 the whole document	1-27

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2001 (2001-11-16), SCHOCH CLAUDIA ET AL: "Specific abnormalities on the genomic level result in a distinct gene expression pattern detected by oligonucleotide microarrays: An analysis of 25 patients with AML M2/t(8;21), AML M3/M3v/t(15;17), and AML M4eo/inv(16)" XP002269491 Database accession no. PREV200200129822 abstract & BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), pages 92a-93a, 43rd Annual Meeting of the American Society of Hematology, Part 1;Orlando, Florida, USA; December 07-11, 2001 ISSN: 0006-4971	1-27
Y	EP 1 043 676 A (WHITEHEAD BIOMEDICAL INST) 11 October 2000 (2000-10-11) the whole document	1-27
Y	GOLUB T R ET AL: "Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 286, no. 5439, 15 October 1999 (1999-10-15), pages 531-537, XP002207658 ISSN: 0036-8075 cited in the application the whole document	1-27
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& BLOOD, vol. 98, no. 11 Part 1, 16 November 2001 (2001-11-16), pages 457a-458a, 43rd Annual Meeting of the American Society of Hematology, Part 1;Orlando, Florida, USA; December 07-11, 2001 ISSN: 0006-4971 ----	
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/012474

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Article 52 (2)(d) EPC - Presentation of information (Claims 22-27)

The claims were only searched with regards to the underlying method of generating a reference data base for distinguishing CBF-positive from

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-27 (partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Article 52 (2)(d) EPC - Presentation of information (Claims 22-27)

The claims were only searched with regards to the underlying method of generating a reference data base for distinguishing CBF-positive from CBF-negative AML subtypes.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-27 (partially)

A method for distinguishing CBF-positive AML subtypes, preferably AML_t(8;21) and/or AML_inv(16), from CBF-negative subtypes, preferably from AML_inv(3), AML_7(15;17), AML_MLL, and /or AML_komplext, the method comprising determining the expression level of the marker CKLFSF4. Use of said marker for the manufacture of a diagnostic. A diagnostic kit containing said marker and an apparatus comprising a reference data bank, wherein the reference data bank is obtainable by determining the expression level of CKLFSF4.

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2. claims: 1-27 (all partially)

Inventions 2-750

Methods for distinguishing CBF-positive AML subtypes, preferably AML_t(8;21) and/or AML_inv(16), from CBF-negative subtypes, preferably from AML_inv(3), AML_7(15;17), AML_MLL, and /or AML_komplext, and methods for distinguishing specific subtypes against all other AML subtypes and against each other, the method comprising determining individually the expression level of the markers listed in tables 1.1, positions 2-50, tables 1.2-1.5 and in table 2. Use of said markers for the manufacture of diagnostics. Diagnostic kits containing said markers and apparatus' comprising a reference data bank, wherein the reference data bank is obtainable by determining the expression levels of said markers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/012474

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